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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

NOVEMBER, 1950

A STUDY OF DIETARY FACTORS, ALCOHOLIC CONSUMPTION AND LABORATORY FINDINGS IN 100 PATIENTS WITH HEPATIC CIRRHOSIS AND 200 NON-CIRRHOTIC CONTROLS

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Recently 900 autopsy records of patients with cirrhosis of the liver coming to autopsy at the Los Angeles County Hospital have been reviewed by Hall, Olsen, and Davis[16]. The lack of detailed information concerning the dietary and alcoholic histories was so striking that a separate study was undertaken in order to obtain these details from living cirrhotic patients. By way of control the dietary regimens and alcoholic habits of 100 non-cirrhotic patients from the author's private practice and 100 non-cirrhotic patients from the Los Angeles County Hospital, have been used for comparison.

Method. One hundred patients in the Los Angeles County Hospital with the diagnosis of cirrhosis of the liver by clinical, laboratory and, in some instances, biopsy findings were examined and interviewed. Cases were excluded in which there was a doubt concerning the etiology of any of the major symptoms or signs of cirrhosis.

Specific questions were asked concerning the kind and the amounts of alcoholic beverages consumed, and the duration of such addiction.

Exact alcoholic consumption was difficult to obtain. Many would deny drinking on first questioning. A few admitted they would drink anything, even "smoke", a thinner for paints and varnish. Alcoholic persons are more likely to underestimate than overestimate their consumption[10]. Variations in the size of drinks, and different percentage of alcohol in whiskey, make necessary the use of such vague terms as "alcohol in moderation", "heavy drinkers", or "alcoholism". Alcoholism was considered present if there was a daily consumption of at least 1 quart of wine, 6 glasses of beer, or 6 ounces of whiskey[32].

Specific questions were asked concerning the daily intake of the essential foods as outlined by Watson[38], MacBride[21], and Pelner[30].

If it was denied that meat was eaten daily, it was asked if eggs, fish, poultry, nuts, or soy bean preparations were eaten on those days. This procedure of questioning was followed concerning each of the essential foods. When it was felt the basic food or its substitutes were lacking it was recorded as a deficiency. A stereotype answer was, "I eat poorly when drinking."

Information about the patient's diet was also difficult to obtain and when obtained was frequently of doubtful accuracy. As Dauphinee and Sinclair[9] suggest, an inquiry should extend to the growing and pre-disease period. Such attempts were soon given up as too impractical and unreliable with the group of patients being interviewed.

Results. Fifty-seven of the patients were males, 43 females; 71 were Cau-

casian, 18 Mexican, 9 colored, 1 Italian, and 1 Chinese. Thirty-five were poorly nourished, 30 were fairly well nourished, 26 were well nourished, and 9 were obese.

The ages ranged from 28 to 76 years, the greatest incidence falling between 40 and 50 years.

The majority of patients consumed a mixture of alcoholic drinks, although 27% stated they drank wine only, and 24% whiskey only (Fig. 1). In 78% the greatest number of patients (45%) were deficient in a combination of protein and vitamin B foods. No deficiencies were elicited in 23% of the patients, and in 13% no history was obtainable.

The protein and vitamin B food deficiencies were so marked in these patients with cirrhosis that it was decided that a comparison with deficiencies occurring in other illnesses might be revealing.

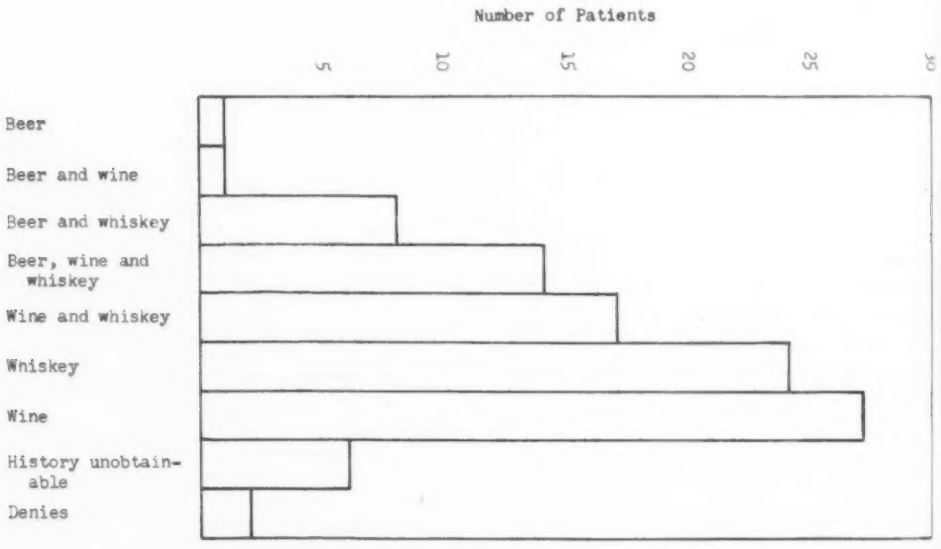

FIG. 1.—Alcoholic beverages consumed.

amounts averaged from 1 pint to 1 quart daily. One patient stated that he drank 1½ gallons of wine daily for 4 years, plus some beer and whiskey. One patient stated that he had drunk 1 pint of gin daily since childhood, another that he drank wine like water. The number of years of heavy drinking varied from 5 to 50 years, the greatest number of patients had been drinking for 15 to 25 years.

The greatest deficiencies were in the vitamin B foods, being present in 60% of the patients. This includes 25% that were deficient in all the essential foods.

One hundred cases (62 females, 38 males) from the author's private practice files were selected at random. Ages varied from 16 to 79 years and represented a wide range of illnesses. Vitamin B deficiencies were also greatest here, but only 20% as compared with 60% in the cirrhotic group. None was deficient in all of the essential foods, as compared with 25% in the cirrhotics. Protein foods were lacking in only 5%, as compared with 45% in the cirrhotics. There were no deficiencies in 25%, as compared with 23% in the cirrhotic group.

A similar group of 100 non-cirrhotic patients (60 females, 40 males) from the Los Angeles County Hospital was analyzed in the same manner, and showed deficiencies similar to the private practice group in protein and B complex foodstuffs (Table 1 and Fig. 2).

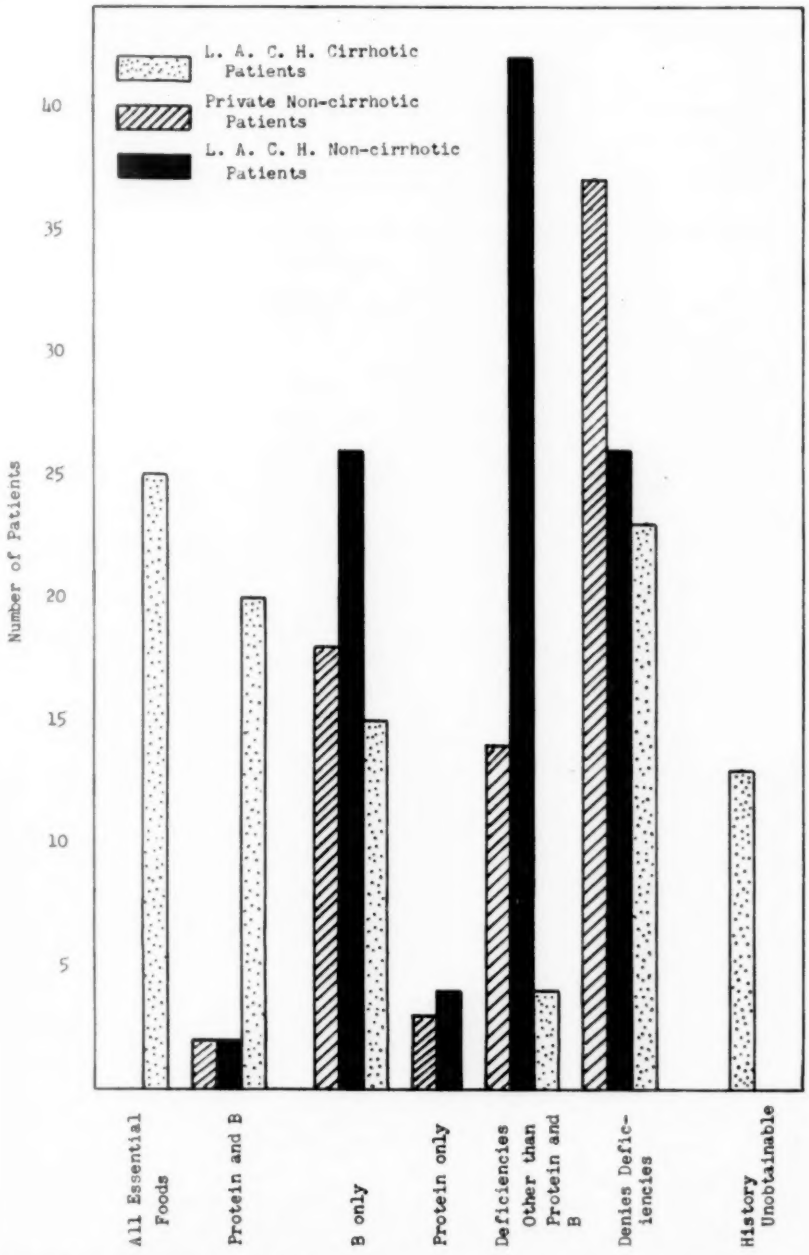

FIG. 2.—Deficiencies of the basic foods in cirrhotic and non-cirrhotic patients.

Alcoholic drinks were taken only occasionally or in moderation by 24% of the private practice patients. The low incidence is partly explained by the greater number of females (62%) in this group. Alcohol consumption was heavy in 5% and moderate in 41% of the non-cirrhotic Los Angeles County Hospital patients. In the cirrhotic group, 78% were heavy and 14% moderate drinkers.

TABLE 1.—SUMMARY OF DIETARY DEFICIENCIES AND ALCOHOLIC CONSUMPTION
(*Expressed in percentages*)

Deficiencies	*Cirrhotics*	*Non-cirrhotics L.A.C.H. Patients*	*Non-cirrhotics Private Patients*
All essential foods	25	0	0
Protein and B complex	20	2	2
B complex only	15	26	18
Protein only	0	4	3
Essential foods other than B complex and Protein	4	42	14
Denies Deficiencies	23	26	63
History unobtainable	13	0	0
Alcoholic consumption	79 (heavy) 13 (moderate?)	5 (heavy) 41 (moderate)	0 (heavy 24 (moderate)

TABLE 2.—ALCOHOL CONSUMPTION, DIETARY DEFICIENCIES AND SYMPTOMS AS NOTED BY VARIOUS AUTHORS
(*Expressed in percentages*)

	Olsen	*Patek*[10] *Post*	*Ratnoff*[3] *Patek*	*Patek*[11] *et al.*	*Kimball*[12] *et al.*
Alcohol consumption	92	54	87	77	79
Deficiencies	64	78	81		
Jaundice	63	65	63	25	80
Ascites	67	78	89	93	77
Esophageal varices	22	27	24	34	29
Spider angiomata	48	33	68	62	37
Edema	48	61	85	69	
Hepatomegaly	86	75	81	79	80
Splenomegaly	16	44	70	55	18

Symptoms, Signs, and Laboratory Data in the Cirrhotic Group. The major signs and symptoms presented by the cirrhotic group were: hepatomegaly, ascites, jaundice, edema, spider angiomata, and hematemesis (Table 2).

There was anemia in 60% of the cirrhotic patients. A leukocytosis was present in 50%; however, 28% had complicating infections, and other causes. No cause for leukocytosis except hepatic pathology was found in 22%. The 22% all showed jaundice, except for 1 patient. Watson[38] states that in "alcoholic" cirrhosis with jaundice there is a group of cases that show a neutrophilic leukocytosis for which no other cause can be found. Since jaundice in these patients is almost invariably accompanied by focal necrosis of the liver, this would explain the presence of leukocytosis[16].

The albumin:globulin ratio was reversed in 58%. Non protein nitrogen was determined in 48 patients and was elevated above 40 mg. per 100 c.c. in 11.

Clinical jaundice occurred in 63% of

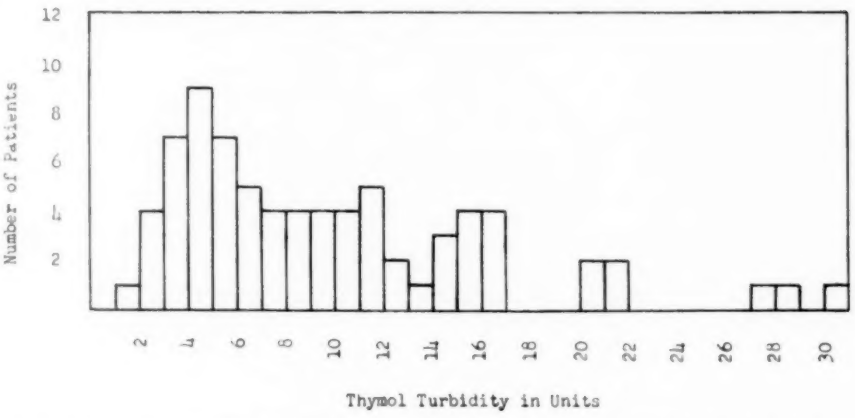

FIG. 3.—58 patients (68%) of 85 cirrhotics showed a thymol turbidity above 4 units.

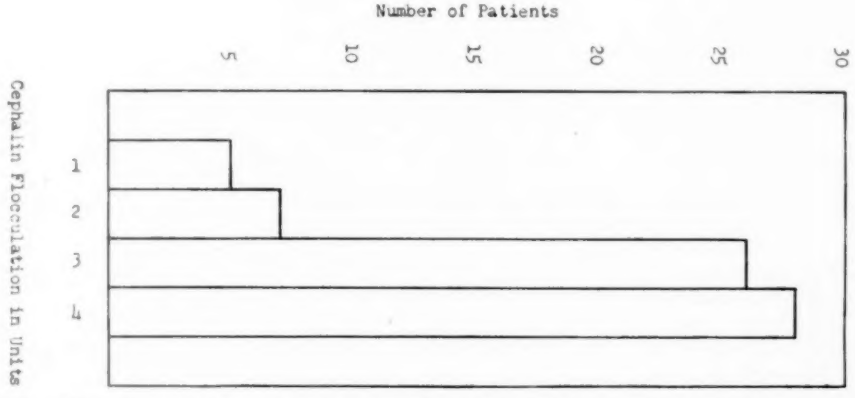

FIG. 4.—66 patients (80%) of 79 cirrhotics showed a cephalin flocculation above normal.

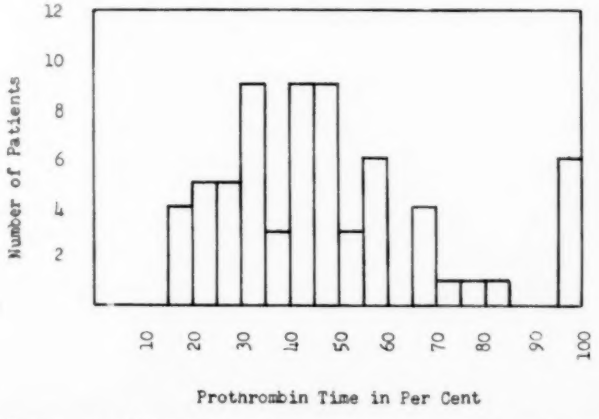

FIG. 5.—53 patients (80%) of 66 cirrhotics were below 70% prothrombin time.

the cirrhotic patients, although icteric indices were above 15% in 72% of the patients. Of the 79 patients in whom icteric indices were done, 76 (92.2%) were above 8 units. In 68.2%, thymol turbidity was above normal, and in 83.5% the cephalin flocculation test was high (Figs. 3 and 4). In 66 patients in whom prothrombin time was done, 53 (80.3%) were below 70% (Fig. 5). Wassermann reaction was positive in 17%. The bromsulphalein test was determined 8 times and was elevated each time. Bile was noted in the urine in 33 patients. Urobilinogen was determined on 36 patients and was elevated above normal in 28 instances. Laboratory data are summarized in Table 3.

TABLE 3.—SUMMARY OF LABORATORY DATA (*Percentages*)

Anemia	60
Leukocytosis	22
Albumin:globulin ratio reversed	58
Non-prot. Nitrogen increased	20
Icteric indices increased	92
Thymol turbidity increased	62
Cephalin flocculation increased	83
Prothrombin time increased	80
Wassermann reaction positive	17
Urobilinogen increased	77

Splenomegaly was found in 16%. Probably a much greater percentage would have been obtained if the technique of Stoll[35] for determining enlargement of the spleen had been known and followed at the time of the examination. Bockus[2] states that the spleen must be 2 or 3 times its normal size before it can be palpated at the rib margin. Splenomegaly is difficult to demonstrate when the abdomen is distended by fluid and gas. Because of difficulties in physical examination the incidence of splenomegaly reported at autopsy is greater than that observed in living patients. Palmar erythema was found in 10%. Skin lesions indicative of a vitamin deficiency were found in 20%. Gynecomastia was noted in 30% of the males.

Alcohol consumption, dietary deficiencies, and symptoms are compared with the findings of others who have made similar investigations[20,28,29,32] (Table 2).

Discussion. Alcoholism causes local inflammatory and degenerative changes of the digestive system. Alcohol causes gastric hyperemia and irritation, first stimulating and then inhibiting secretions. Long continued use results in chronic catarrhal gastritis, achlorhydria and enteritis. This frequently results in anorexia, vomiting, gastric hemorrhage, abdominal distension, and diarrhea[1,23,31,33].

Alcoholic addicts notoriously develop nutritional deficiencies and electrolyte imbalances. There is poor intake of food; vomiting and diarrhea. Most of the calories consumed are obtained from the non-nutritional alcoholic beverages[22]. When 1 gm. of alcohol is oxidized in the body to carbon dioxide and water it furnishes 7 calories to be used by the body for energy, and energy only. It is not stored in the body, nor does it build new tissue[13]. One pint of whiskey, containing 50% alcohol, furnishes 2000 calories. Thus in the alcoholic a high intake of such calories contributes to a poor appetite[15]. Gastro-intestinal abnormalities, particularly gastritis, achlorhydria, and enteritis also cause anorexia and alteration in the metabolism of essential food elements. Thus closely related to alcoholism are neuritis, pellagra, beri-beri heart, and cirrhosis of the liver[27,33].

It is frequently asked, why does one man who has been a daily consumer of alcoholic beverages for many years reach a ripe old age and succumb with no inflammatory or degenerative changes due to the use of alcohol while another man, in early adult life, suffers impairment of one organ or another after a comparatively short use of the same intoxicants? There

must be a constitutional predisposition, an original inferiority of an organ, plus the economic status, and the nutritional state, that makes such an individual susceptible to the effects of alcohol[36].

Hall and Morgan[15] attempt to answer this question. They state that 20 to 25 years of drinking, with a lowered intake of foods and vitamins, alter the metabolism of protein and fat, decrease glycogen within the liver cells and increase the fat content. The liver is thus made vulnerable to mild hepatic poisons such as alcohol. They conclude that there is an individual idiosyncracy coupled with a lowered intake of food and a deficiency of certain vitamins which injure the liver cell so that a mild hepatic poison produces the changes seen in cirrhosis. Others have emphasized the role of fatty metamorphosis in producing hepatic fibrosis[6,18]. Boyd[4] states that low protein intake associated with deficiency of the vitamin B complex leads to liver necrosis followed by periportal cirrhosis. Others have also suggested that hereditary liability and dietetic factors render the liver vulnerable to mild toxic substances such as alcohol and to virus infections which result in liver damage[3,18,28,32,34,37]. Our findings seem further to substantiate evidence both experimental and clinical, which suggests that portal cirrhosis has as its basis a multiple nutritional deficiency, chiefly of protein and the B complex foodstuffs and that alcohol is probably a significant indirect causative factor insofar as it causes faulty dietary habits[3,5,7,11,12,14,17,19,24,25,26,29].

The above findings suggest that improvement in prognosis may be brought about by the application of the therapeutic concepts laid down by Patek[28] which consist principally of a diet rich in protein and vitamin B complex. This has recently been well outlined by Dauphinee and Sinclair[9], Patek *et al.*[29], Ratnoff[32] and Morrison[26].

Summary. One hundred patients with portal cirrhosis of the liver were interviewed and examined. Our findings, with minor variations, coincide with those of others who have made similar investigations.

One hundred non-cirrhotic patients from private practice of similar age groups and 100 non-cirrhotic patients in the Los Angeles County Hospital were interviewed as to alcoholic consumption and dietary deficiencies. Alcoholic drinks were taken only occasionally or in moderation by 24% of the private practice patients. Alcohol consumption was heavy in 5%, and moderate in 41% of the non-cirrhotic Los Angeles County Hospital patients. In the cirrhotic group, 78% were heavy, and 14% moderate drinkers, according to their own statements.

The most common dietary deficiencies consisted of a combination of protein and vitamin B complex foodstuffs, which occurred in 45% of patients, while 15% were deficient in B complex only. There was thus a B complex deficiency in a total of 60%. This figure is probably low, as no history was obtained from 13 patients. It was felt that it was significant that there was a combination of protein and vitamin B complex deficiency in the non-cirrhotic groups of only 5% and 6% respectively, as compared with 45% in the cirrhotic group.

Nutritional deficiencies and alcohol as factors in the etiology of cirrhosis of the liver are discussed.

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PARKINSONIAN TREMOR, MANIC-DEPRESSIVE PSYCHOSIS AND SERVOMECHANISMS

By Eric Barrett, L.L.D., M.D.
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The mechanisms underlying Parkinsonian tremor as well as manic-depressive psychosis are still largely obscure. The hypotheses presented here with regard to their mechanisms are offered in order to suggest certain analogies between phenomena from the field of the exact sciences on one hand and the biological sciences on the other, as well as between neural functions on different levels of integration.

Wiener, McCulloch and a number of other forward looking scientists[7,22] have recently proposed a new approach to the solution of problems in physiology, psychology, sociology and many other related fields by applying to them some of the principles of control- and communication-engineering. They suggest the name "cybernetics" for this compound science.

The following is an attempt in the same direction, that is, the presentation of hypotheses for the mechanism of certain functions and dysfunctions of the nervous system by applying to them some principles of so-called servomechanisms.

One example for such an analogy is Parkinsonian tremor, a neurological disorder on the lower levels of central integration, that is, predominantly between the spinal cord and the basal ganglia. Another example is manic-depressive psychosis, a psychiatric disorder on the predominantly highest, the cortical level.

Servomechanisms are devices designed to serve specific purposes of control or communication, such as thermostats, automatic pilots in airplanes, mathematical computers and many others. Considering the purposes for which such servomechanisms are designed, it seems useful to distinguish two kinds: One has as its main task the computation of data from information fed into it. It may be a device to solve mathematical problems, to calculate the position and the firing time of anti-aircraft guns, or to locate a speeding submarine. Because its goal is varying, changing and frequently moving, we may call this kind of servomechanism a *teleodynamic servo.*

The other kind is concerned principally with the maintenance of a condition, such as the level of temperature, the steady flow of a gas, a liquid or of electricity, the balance of an airplane, or the course of a ship. Since its goal is the steadiness of a condition, the stability of an equilibrium, we may call it a *teleostatic servo.*

The human brain must be considered as serving both purposes and therefore combining both mechanisms. Through teleodynamic mechanisms we find our goals in the manifold situations of life, we arrive at equilibria with confusing and conflicting environmental forces. Through these same teleodynamic mechanisms we build our attitudes, synthesize our egos and form our personalities. Through teleostatic mechanisms we try to maintain those attitudes and equilibria that are the goals and ideals for which we live, the roots for our decisions, the basis for all behavior and voluntary activities.

The most characteristic element of a teleostatic servo is the so-called nega-

tive feedback, the report from a sensing or measuring device to the regulator about the state or condition to be maintained. Such a sensing device for the maintenance of a straight course of a ship may be a compass, for the maintenance of a temperature level a thermometer or other temperature recording instrument. Because of the effect of their report upon the regulator that corrects and reverses the flow of activity under control, it is called a negative or inverse feedback. A deviation from the goal is thus fed back to the regulator, which reverses the flow. The momentum carries the activity beyond the goal until its inverse deviation is again sensed, fed back and corrected. Like a pendulum this oscillation around the goal would go on infinitely unless "damped" by friction. It is important to keep in mind that oscillations round the goal are an intrinsic, potential part of every balancing or maintenance mechanism, or, in our terminology, of every teleostatic servomechanism.

The amplitude, the frequency and the number of oscillations depend upon the construction of the sensing device and upon the damping action. The sensing instrument can be designed to perceive the degree of deviation in advance and thus permit a speedier and more successful correction. We employ similar functions in driving a car. A beginner will notice a deviation too late. He may overshoot his correcting movements and send the car into a swerving motion. The experienced driver will not wait until the momentum has carried his car into the wrong direction, but will sense the deviation in advance. He also knows that a certain friction in the steering wheel increases the steadfastness of the car. The correct amount of friction or damping may decrease or eliminate oscillations.

Without going into details of a very complex and highly mathematical branch of engineering, we can easily see that a well constructed and well functioning feedback mechanism may avoid the intrinsic oscillations of a teleostatic servo, or reduce them to a minimum, while its defect will determine the duration, rate and degree of these oscillations around the desired state.

We shall now attempt to apply these simple observations to certain dysfunctions of the nervous system.

Parkinsonian Tremor. This tremor is also known as static, postural or rest tremor and is characterized by about 4 to 10 alternating impulses per second that are strongest at rest and diminished or abolished by voluntary activity, in contrast to action or intention tremor that occurs only during volitional movement. A number of facts regarding postural tremor are known on the basis of experimental and clinical findings[9].

The so-called myotatic unit, which includes facilitations of synergists and inhibitions of antagonists, in other words, all the reciprocal innervations necessary for the maintenance of posture, is a mechanism that is integrated on the spinal level[11].

The reticular formation caudal to the basal ganglia consists of facilitatory and inhibitory components affecting the amplitude of movements however evoked[14,19]. It is here, and particularly in the lower portion of this reticular formation, that one can look for the amplification of alternating impulses, resulting from reciprocal innervation.

The synchrony of such alternating impulses, innervating the anterior horn cells, is maintained as long as they are undisturbed by asynchronous impulses due to voluntary movements or from any other source. The intactness of the whole pyramidal tract has been found necessary for certain postural activities, including postural tremor[15,23].

The extrapyramidal system has mainly regulatory functions with regard to posture, in particular suppressor functions[12,17]. The inhibitions seem to have the effect of "damping" the oscillations. In man the main center for such damping inhibitions is apparently the substantia nigra (zona compacta) and, or, the globus pallidus[5]. In monkeys it may be the mesencephalic tegmentum below the basal ganglia[19]. Stimulation of the basal ganglia does not produce movements. They are, however, themselves suppressed by the cortex, since their spontaneous electric discharges are of small amplitude, while after removal of all cortical connections their activities show a high voltage. A well-organized topographical projection seems to exist between the cortex and the basal ganglia[6]. Areas 8s, 4s, 2s, and probably 19s, activate the nucleus caudatus, 8s its head, 4s its middle region, and 2s the tail. Areas 6 and 4 activate putamen and globus pallidus.

Deficiency of the principal "damping" centers may make the oscillations manifest. The destruction of still "higher" structures, such as the corticonigral or cortico-pallidal fibers of the so-called parapyramidal tract, may thus release other vicarious suppressor areas in still intact basal ganglia and therefore exert a favorable influence on the tremor, without paralyzing normal motor functions.

Such an interpretation of the factors leading to Parkinsonian tremor and its abolition would comply with surgical experiences and experimental facts.

MANIC-DEPRESSIVE PSYCHOSIS. This mental disorder is presented here as a defect in the teleodynamic and teleostatic adjustment mechanisms of an individual to his environment. These adjustment mechanisms cannot be explained in this brief paper, but an attempt to do this somewhat comprehensively has been attempted by the same author in 2 articles[1,2], abbreviated treatises preliminary to a book, The Biology of Human Motivations, that is still in preparation. According to this author's viewpoint, the process of coping with the variety of changing forces of our surroundings involves the *teleodynamic mechanisms of finding* attitudinal equilibria with these forces and the *teleostatic mechanisms of maintaining* them. By equilibria is meant the whole of an individual's attitudes toward the different environmental forces.

The *teleodynamic* mechanism of finding, or of the computation, of such attitudinal equilibria signifies the egosynthesis or personality formation. Obviously this process is a slow one in which innumerable factors of exogenous and endogenous nature play a part.

The *teleostatic* mechanism of maintaining these attitudes in the face of changing and varying stimulations from the surroundings, in particular with regard to the social or personal environment, contains, like every other teleostatic mechanism, the predisposition and condition for oscillations round the goal, in this case for "personality tremor".

It is the function of the feedback mechanism that determines whether only one deviation from the desired state occurs, or whether this deviation is followed by an overshooting in the opposite direction, or whether a whole series of oscillations occurs.

Since the process of attitude and personality formation is very slow, a personality tremor must be correspondingly slow. As so many factors play a part in this process, it is understandable that the oscillations may in some cases be regular and in others quite irregular. We know that all these cycles actually take place in manic-depressive psychoses and that the individual attacks may last a few weeks or a year,

or, on the average, a few months[13].

The manifestation of this disorder would thus have to be subject to an analysis in every single case. This presentation merely points out the fact that all forms of clinical cyclothymia or manic-depressive psychosis can be explained along the lines of this proposed hypothesis.

Discussion. Among the most outstanding features of the manic state may be mentioned: A general hyperactivity; strong reactivity to environmental stimulation and lack of concentration, leading to flightiness of thought; lack of criticism and consciousness of the self; lack of inhibition.

The depressive state is characterized by the opposite features: Too much concentration on and concern about the self; indifference towards the environment and, in extreme cases, stupor and neglect of the environment and the self[4].

The synthesis of coordinated reactions and attitudes to the environment must be regarded as a cortical function. The above mentioned activities seem to point predominantly in the direction of the frontal association areas. In particular the rostral cingular and the orbito-frontal cortices have been associated with general activity and with social behavior[10,16,20,21]. The concern with the self and other functions in connection with self-consciousness have been traced to the base of the frontal lobes by Freeman and Watts[8], who also think that the frontal lobes mediate functions of foresight and insight, that is, the essentials of a critical attitude.

Studies of the effect of "psychosurgery" such as the 1000 British leucotomies[3] will no doubt contribute to our knowledge of the anatomy and physiology of behavior.

If we believe that depressions are caused by too much concentration on the self, and the frontal lobes are concerned with self-consciousness, the change of such preponderant conduction patterns by frontal lobotomies would explain the excellent success of this operation, which, according to studies such as the above[3], or those of Van Wagenen[18], is considered "specific for depressions". Here experimental facts seem to correspond with theory.

As for the mechanism of the oscillations round the desired state, or the "personality tremor" constituting manic-depressive psychosis according to this hypothesis, it should be kept in mind that it is mainly the alternating changes that have a similarity with postural tremor because both disorders are considered to be based on teleostatic systems. Even these alternating changes occur in only a fraction of manic-depressive disorders. In most other respects there are more differences than similarities between the two dysfunctions. As has been stated, postural tremor is a feature of the lower levels of central integration, while manic-depressive psychosis is one of the higher levels.

Concerning the mechanism of the oscillations, rest tremor seems to be mainly the result of defective damping. There are damping inhibitions too in the adjustment processes to the environment. They are to a large extent produced by the teleostatic mechanisms of society, such as education and law enforcement.

There is sufficient evidence from animal experimentation, as well as from the results of surgical operations in man, that there are also anatomically defined structures in the brain that deal with inhibitions of thoughts and overt behavior. Lesions of these structures by surgery or certain degenerative pathological processes of the central nervous system may cause an impairment of inhibitions. However, the lack of damping inhibitions

is probably not the only factor for the appearance of cyclothymic disorders. The construction of the sensing devices in teleostatic systems also plays a part in the occurrence of oscillations. These sensing devices correspond in the brain with the structures and conduction patterns mediating the perception of our own activities, self-criticism, insight and foresight, in other words functions which have also been traced to the frontal lobes and which are the teleodynamic functions of finding attitudes and equilibria and of discovering the deviations from them.

It is most likely that a defect in these teleodynamic functions is at the root of cyclothymic disorders, besides the lack of inhibitions.

This analysis is obviously presented not as the solution of problems but only in the hope that the pursuit of this train of thought may provoke inquiry.

Summary and Conclusions. In order to explain the mechanisms of Parkinsonian tremor and manic-depressive psychosis, analogies have been applied between these functions of the central nervous system and certain principles from the field of control- and communication-engineering. So called servomechanisms have been divided into teleodynamic and teleostatic types. An intrinsic feature of teleostatic mechanisms is the oscillation round the goal or desired state, which becomes manifest as the result of defects of the feedback systems.

Parkinsonian or rest tremor has been explained as resulting mainly from lesions in damping inhibitors in the basal ganglia, manic-depressive psychosis as the result of defects in the formation of attitudinal equilibria, the maintenance of which belongs to the essential adjustment mechanisms of an individual to his environment.

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EFFECT OF DESOXYCORTICOSTERONE AND ASCORBIC ACID ON RHEUMATOID ARTHRITIS*

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Dramatic clinical improvement in patients suffering from rheumatoid arthritis given 5 mg. of desoxycorticosterone intramuscularly followed by 1 gm. of ascorbic acid intravenously was reported by Lewis and Wassen in November, 1949[11]. Since then conflicting reports concerning the efficacy of this combination of agents have appeared[2-10,12-16,18]. However, controlled and objective studies have not been published, and for this reason we undertook a study under such conditions in 5 patients with rheumatoid arthritis who had been under observation for a considerable period of time. Thus it was possible to evaluate any change in their progress attributable to a specific therapeutic procedure.

No physician treating patients with rheumatoid arthritis today is unaware of the interest aroused in these people by the reports in the lay and scientific press of the rapid remissions induced by ACTH and cortisone. As a consequence, any change from the usual arthritis routine is greeted with interest and the patients eagerly look for any evidence of improvement. Because we had observed what we thought to be a rather dramatic response in one of our patients to a test injection of desoxycorticosterone and ascorbic acid, we felt that it would be essential to the successful evaluation of the treatment to make our observations as objectively as possible.

Method. The patients were continued on their usual therapy of analgesics as required, physiotherapy and the ward routine of graded activity. The diet was changed from a house tray to one in which the sodium content was maintained at 8 gm. per day as NaCl: this represented little reduction from the standard diet but did insure against intake above that level. Observations of weight, fluid intake and output, and blood pressure were made daily. In addition, the impression of the physician as to the patient's emotional status, objective changes in the joints, and measurements by goniometer of a major affected joint, were recorded. Prior to therapy, an electroencephalogram, roentgenograms consisting in a 6-foot P.A. of the chest for cardiac diameter and a film of one major joint, and photographs with a double exposure technique demonstrating full extension and flexion of an involved joint, were made. At weekly intervals these were repeated, if changes were observed, and all were obtained at the termination of the treatment period.

Complete blood counts together with hematocrits and sedimentation rates were made every other day. Twice weekly serum sodium, potassium, uric acid, sugar and ascorbic acid levels were obtained. Once a week the response of the blood eosinophils

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to the injections was determined, together with an estimation of the ratio of urinary uric acid/creatinine excretion in the 2 hour period before medication and the 4 hour period immediately following. The amount of 17 ketosteroids in a 24 hour urine was determined once weekly.

Medication. Stoppered bottles, labeled only by number, were prepared in the hospital pharmacy, one series containing 100 mg. of ascorbic acid per cc., a second containing normal saline, a third containing 5 mg. of desoxycorticosterone in 1 cc. of sesame oil, and a fourth containing 10 mg. of cholesterol in 1 cc. of sesame oil. These were issued to the wards without either the nurses or the physicians knowing their contents. At 8:00 a.m. each morning the oily solutions were administered intramuscularly by the nurse, and between 5 and 10 minutes later the ascorbic acid or saline was given intravenously by the doctor. The key to the combination of drugs was known only to one of us.

Four weekly periods were studied, with the following combinations: Period A. 5 mg. desoxycorticosterone and 10 cc. normal saline; period B. 10 mg. cholesterol and 10 cc. normal saline; period C. 10 mg. cholesterol and 1 gm. ascorbic acid; and period D. 5 mg. desoxycorticosterone and 1 gm. ascorbic acid.

Case Reports. CASE 1. C. B., a 33-year-old white male, developed aching in his feet in October of 1947. He was hospitalized in August, 1948, and treated with salicylates, gold, and intravenous typhoid vaccine. In spite of this therapy, he became progressively worse with involvement of both elbows, hands, shoulders and jaw. His joints became red and painful, and he developed psoriatic skin lesions on his legs and toes. He was transferred to this hospital on April 12, 1949.

Physical examination at that time showed a markedly underweight male with generalized muscular atrophy. The knees, ankles, wrists and elbows were enlarged, tender, warm and painful. Motion was limited. Dorsal surface of hands showed marked atrophy and fusiform swelling of the fingers.

Sedimentation rate was 28 mm. and Roentgen-ray films showed severe polyarticular rheumatoid arthritis.

During his hospitalization he has been given physiotherapy, salicylates and supportive measures without relief or improvement. He was placed in the study group and no improvement was observed.

CASE 2. C. G., a 57-year-old white male, developed swelling and pain in his ankles and left knee in April, 1949. This became progressively worse and his hands, elbows and shoulders became stiff and sore. He was treated with gold, blood transfusions, physiotherapy, intravenous procaine and salicylates with only slight improvement. He was admitted to this hospital on November 3, 1949.

Physical examination showed a well developed male with thickening of elbow and wrist joints, swelling of the proximal interphalangeal joints of both hands and slight swelling of both ankles and wrists.

Sedimentation rate was 36 mm.

The patient received physiotherapy, salicylates and the usual ward care. There was little improvement noted. He was placed in the study group and no response was observed to the therapy.

CASE 3. F. M., a 56-year-old white male, noted gradual onset of stiffness and pain in most of the joints 14 years ago. It progressed to involve, ultimately, most of the joints of the body. The pain was increased by motion and weather change. In the recent months, most of the pain has been in the knees, shoulders, and neck.

Physical examination revealed a well developed, moderately well nourished white male. There were marked joint deformities of both upper extremities, with limitation of motion, and ulnar deviation at the wrists and in the fingers. Flexion contracture of both hips was present. Both knees were swollen; motion was limited and was accompanied by marked crepitation.

Sedimentation rate was 33 mm. in one hour.

The patient was placed on the usual routine of physiotherapy and salicylates. With this therapy and traction he showed very gradual but slight improvement. He was placed in the desoxycorticosterone and ascorbic acid study group for a 4-week period. There was no improvement.

CASE 4. A. N., a 45-year-old white male, had the onset of swelling and pain in the toes of feet in March, 1947. Within 1 month and progressively thereafter the hands, fingers, knees and ankles became involved: subsequently the pain involved all joints. Treatment prior to admission to this hospital in April, 1949, had included antibiotics, a course of typhoid induced hyperpyrexia and one injection of gold.

Physical examination on admission showed all the joints to be involved. The knees were slightly swollen and tender. Motion was limited. The ankles were tender with limited motion. Toes were ankylosed. The fingers were flexed at the metacarpal phalangeal joints. The wrists were ankylosed with ulnar deviation. The elbows were indurated and tender. Motion of the right knee by goniometer was 175° to 50° (See Figs. 1 and 2).

FIG. 1.—Patient A.N. Double exposure photograph of right leg in full extension and full flexion. Motion 100° Taken Jan. 23, 1950, prior to treatment.

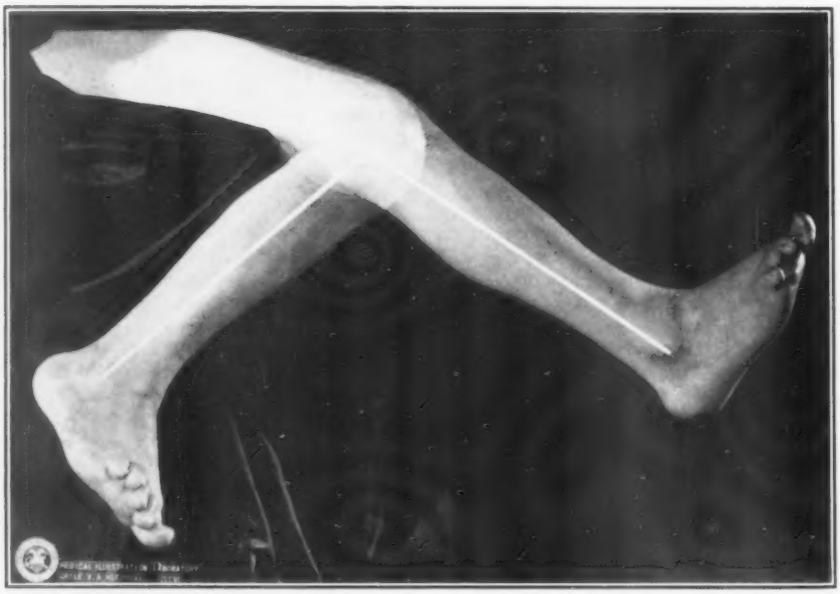

FIG. 2.—Patient A.N. Photograph of right leg. Motion 105°. Taken Feb. 28, 1950, after one week of DOCA and ascorbic acid.

TABLE 1.—CASE A. N. SUMMARY OF CLINICAL OBSERVATIONS AT BEGINNING AND END OF EACH STUDY PERIOD

Periods	*A*		*B*		*C*		*D*	
Days	1	7	1	7	1	7	1	7
Weight	136	138½	137¾	138½	137	137¾	138	137½
Motion rt. knee	170°–50°	175°–50°	175°–50°	175°–50°	175°–50°	175°–50°	170°–50°	170°–50°
Swelling	2+	2+	2+	2+	2+	2+	2+	2+
Mental	Euph.	Euph.	Euph.	Euph.	Euph.	Euph.	Euph.	Euph.
Cardiac dia./Chest dia.		13.2/29.7		14.6/30.1		13.7/30.4		13.5/29.8
B. P.	110/58	95/68	88/60	88/60	104/68	104/70	100/80	104/70

Period A: 5 mg. desoxycorticosterone and 10 cc. normal saline
" B: 10 mg. cholesterol and 10 cc. normal saline
" C: 10 mg. cholesterol and 1 gm. ascorbic acid
" D: 5 mg. desoxycorticosterone and 1 gm. ascorbic acid

TABLE 2.—CASE A. N. SUMMARY OF LABORATORY OBSERVATIONS AT BEGINNING AND END OF EACH STUDY PERIOD

Periods	*A*		*B*		*C*		*D*	
Day	1	7	1	7	1	7	1	7
Sed. rate	16	32	32	33	37	22	28	31
Hematocrit	38	38		42	38	38		39
W. B. C.	5900	6200	6700	6000	5850	7900	7100	7400
Neutrophils	81	67	58	57	52	42	62	59
Lymphocytes	18	38	32	32	46	49	26	29
Eosinophils	1	1	3	8	6	6	1	3
Basophils			2	3		3	8	
Monocytes			5		2		3	9
17 K/S mg./24 hr			15.4			7.0		9.86
NA m.Eq/L		144.5	144.5	143.5	147.0	142.6	145.8	145.9
K m.Eq/L		3.95	6.6	5.33	6.05	4.44	4.68	4.41
Uric acid mg./100 cc	5.0	6.1	8.6	5.61	3.63	5.9	4.20	6.16
Sugar mg./100 cc					71	65	77.1	70.2
Uric acid/Creatinine		+40%		+33%				−50%

Laboratory studies: See Table 2.

The patient received salicylates, physiotherapy, and 300 mg. of gold. However, this had little or no effect. He was placed in the special study with desoxycorticosterone acetate and ascorbic acid. During the 4 weeks of treatment there has been no essential change in his condition (Table 1).

CASE 5. K. J., a 58-year-old white male, began to have pain in the left foot and knee in the fall of 1947. He then developed pain in the right knee, right ankle, and metacarpal arches. The pain was considerably worse in bad weather. He was hospitalized in March, 1948, when he was given deep diathermy, and 1000 mg. of gold. This alleviated the pain to a sufficient degree so that he was able to work. He apparently developed no toxic symptoms from the gold. The pain became progressively more severe recently, and therefore he sought hospitalization. He was admitted to this hospital on November 3, 1949.

Physical examination showed a well developed and fairly well nourished white male who stood in a stooped position, due to contractures, and could not walk without help. Both knees were swollen but not reddened or hot. They were painful on motion, and both felt doughy. The hands showed slight thickening of the metacarpal phalangeal joints with limitation of motion. There was limitation of motion in the right shoulder. The motion in the right knee, as measured by goniometer, was 155 to 70°.

Sedimentation rate was 24 to 40 mm. in 1 hour.

The patient was placed on physiotherapy and given salicylates; with this treatment he slightly improved. He was placed in the study group and there was no subjective or objective improvement during the total period.

Results. None of the patients demonstrated any significant response to

the combinations of the drugs administered. One patient (A. N.) felt that he had benefited somewhat from the treatment but stated that this improvement was associated with the beginning of the period of observation and presumably was a psychological response to the special attention of the study group. Table and photographs summarizing the clinical and laboratory data on this patient are included to demonstrate the methods of observation; the data from all 5 patients were similar.

Of interest is the fact that there was no significant physiological effect from desoxycorticosterone in the 5 mg. dosage used.

Discussion. Since the original publication by Lewin and Wassen of their observations on the beneficial effects of this treatment, there have been 15 reports of the experiences of various authors. Improvement of a greater or less degree has been claimed for 179 patients, chiefly rheumatoid arthritics, and failure of response noted in 43. The reports available have been very meager as to details of selection, methods of control and observation, and case descriptions. As a consequence, any attempt at analysis of the results of other observers would be purely speculative. However, it is difficult to reconcile our own complete failure to observe improvement in any of our patients with the enthusiastic reports of several authors. Loxton and LeVay[12], as a result of observations made on several of their patients, offered as an explanation for the failure to obtain a satisfactory therapeutic effect by other workers, the administration of the desoxycorticosterone subcutaneously rather than intramuscularly. This criticism was kept in mind by us and the desoxycorticosterone was therefore given deep into muscle tissue. Similarly the same authors[13] considered that the failure of Spies *et al.*[18] to obtain a response was due to a limitation of salt intake with a consequent change in the reactivity of the "end organ". We believe this possibility was controlled in our study by the maintenance of a normal level of electrolytes in the bloods of all our patients during the observation periods. The salt intake was not unduly restricted as compared to the normal diet of this hospital.

G. Brownlee[1] on the basis of observations made on rats using the formaldehyde arthritis technique of Selye[17] concluded that quantities of desoxycorticosterone in excess of an optimal amount competed with the natural "anti-arthritic steroid" for ascorbic acid and made the arthritis worse. He suggested that Spies and his co-workers failed to obtain improvement because their dosage of 10 mg. of desoxycorticosterone supplied an excess of the hormone. The dosage used in our study was at the 5 mg. level suggested by the original authors: the failure to demonstrate weight gain or hypernatremia is in our opinion good evidence that in the amounts given there was no demonstrable physiological effort from the material, and it is very doubtful that even at the 10 mg. level as used by Spies an excessive quantity of hormone is supplied to the normal individual with intact adrenals.

Fox[5] defined rheumatoid arthritis as a clinical entity characterized by a prodromal period of fatigue, migratory pains and muscle stiffness, vasomotor disturbances and tachycardia. Anorexia and weight loss soon follow and the diagnosis is made when joint involvement with swelling, pain and limitation of motion develops. There is an increase in the sedimentation rate and usually a microcytic anemia. It is in this group that he suggests a true hormone deficiency exists and in which benefit from hormone therapy

can be expected. He states that from a study of 30 cases he has evidence supporting this concept, together with observations indicating that failure to improve can be expected in those patients with arthritis not associated with the rheumatoid syndrome, since in them no hormonal deficiency exists. Our 5 patients were all typical cases of rheumatoid arthritis fulfilling most or all of the above criteria. Failure occurred in all 5 and we must conclude that desoxycorticosterone and ascorbic acid in combination is not adequate replacement therapy for an effective steroid.

Conclusion. Under carefully controlled conditions of treatment no beneficial effect from desoxycorticosterone and ascorbic acid was demonstrated in 5 patients with rheumatoid arthritis.

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STUDIES OF PALMAR HAND SWEAT IN HEALTHY SUBJECTS AND IN PATIENTS WITH NEUROCIRCULATORY ASTHENIA (ANXIETY NEUROSIS, NEURASTHENIA, EFFORT SYNDROME) WITH A DESCRIPTION OF A SIMPLE QUANTITATIVE METHOD

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Excessive moisture of the palms has been regarded, traditionally, as a sign of "nervousness" and as an indicator of "stress"[19,23]. It has also been described as a feature of neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome)[1,9,10,20,28,33,34]. The clinical statements have been based on clinical observations, or on non-quantitative or indirect estimations of palmar sweat. Some of the statements about "mental sweating" are based on the results of complex quantitative methods[19]. It was deemed necessary to devise a method that would be both quantitative and simple for studying amounts of palmar moisture. The method finally used consisted of weighing, on a sensitive analytical balance, the amount of moisture absorbed by an absorbing unit from the palm of the hand[4]. This report describes the details of the method and some of the measurements by this method of palmar sweat in healthy control subjects and in patients with neurocirculatory asthenia.

Methods and Procedure. *Technique of Measuring Palmar Moisture.* Briefly, this technique included weighing on a chemical balance a good quality blotter of specified size and composition, placing it on the palm for 1 minute, and then weighing again. The amount of gain of weight of the absorbing unit (blotter) is referred to as the amount of palmar "moisture" or "sweat" per absorbing unit and minute.

A projection-reading analytical balance, Christian Becker Chainomatic No. 911, was used[30]. It was damped, and read to .0001 gm. on an illuminated scale. The damping and the illuminated scale provided for rapid weighings: the former eliminated prolonged swinging, and the latter eliminated the time required for adding additional weights for the second weighing.

The absorbing units were blotters (120 pound index paper coated on one side, white on white) cut commercially into squares of 2.2 inches by 2.2 inches (5.6 x 5.6 cm.), the area of the absorbing surface was about 31.6 cm^2, and the thickness of the blotter about .5 mm. Blotters from the same lot were used over a period of 6 years and were stored in a covered paper box under room conditions.

The absorbing units (blotters) were placed on a watch glass on the balance, the weights were arranged so that the initial and final weighings were on the positive side of the illuminated scale. The absorbing units weighed about 1.1600 gm., there being a variation from that average weight of about $\pm$ 15 mg. The blotter was picked up by forceps and placed on the palm of the patient's hand with the examiner manipulating the coated side. The blotter was stroked and pressed gently against the palm for 1 minute as determined by an accurate stop-watch. The blotter was immediately transferred by forceps to the balance, and weighed again. The difference between this weighing and the initial one was referred to as the weight of hand sweat or palmar moisture. The transfer and reading were done as quickly as possible, the average

• Work supported by research grant from the Medical Department, U. S. Army; with the cooperation of the Veterans Administration. This work was done with the technical assistance of Jane R. Brown, Mary L. English, Alice E. Dash and Eleanor W. Reed. Dr. Jane Worcester advised on statistical methods.

time for a reading being about 15 seconds, about 10 seconds of which were used by the balance in coming to equilibrium. In some tests one observer did both manipulation and weighing, in others one observer manipulated the blotter and the other did the weighing.

The subject sat in an easy chair, palms supine for 5 minutes, before the procedure. Room temperature was recorded. The relative humidity was determined by means of a sling psychrometer and values recorded were from standard tables[18].

Patients and Control Subjects. The patients were 33 men diagnosed neurocirculatory asthenia who had been under psychiatric or medical care in service hospitals. They were all in military service. Their mean age was 26.79 years. Criteria for diagnosis in this group have been described elsewhere[3,7,8]. The patients were sent to this laboratory for special study.

Healthy control subjects consisted of 54 men in military service who were sent to the laboratory for special study as control subjects. Their mean age was 23.74 years.

In addition, 30 men who were hospital workers were used as controls in order to test the possible influences of familiarity with hospital surroundings and procedures on this determination, as the men in this group were familiar with this hospital while the members of the above 2 groups were not. This group included maintenance workers (plumbers, sheet-metal workers, steam-fitters, electricians, welders) and physicians (medical students, graduate students, internes and staff physicians). The mean age of this group was 29.5 years.

Procedure. All reported determinations were made in the laboratory under ordinary room conditions.

Studies included estimating the variations in weight and size of blotters, estimating the speed of making the determination, determining the speed of evaporation of moisture from the absorbing unit, testing for possible gain of weight of the absorbing unit from the examiner's fingers, evaluating possible effects of room conditions, that is, temperature and relative humidity, on the measurements by estimating the correlation between these measurements and room temperature and relative humidity[21,22].

Determinations of hand sweat were made in patients and in control subjects under similar laboratory conditions; measurements of right and left hand moisture were done in all subjects. The mean values of the hand sweat of the initial determinations were calculated, and the difference between the means of various groups were compared statistically from calculations of the standard error of the difference between means[17,29]. The mean values of determinations of hand sweat of the right and left hands were compared in each group and the results were analyzed statistically, comparing both the differences within each of the 3 groups of patients and the difference between right and left hands of one group compared with that of another group. A significance ratio of 2 or over, corresponding to odds of about 20 to 1 or over[29], was considered significant.

Determinations of values of hand sweat in other conditions were made, and a few of these determinations in special conditions in which hand sweat is of special interest were included in this report in order to add a broader clinical base-line to the evaluation of the technique and its possible usefulness.

Results. THOSE RELATED TO THE TECHNIQUE OF MEASUREMENT. *Variation in weight of absorbing unit.* The mean weight of 30 blotters was 1.1594 gm.; the range was 1.0834 to 1.1864 gm. with a standard deviation of ±.020661 gm. and a standard error of ±.00384, coefficient of variation 1.80. Twenty consecutive blotters showed a mean deviation from the previous one used of ±.0146 gm.

Variation in area of absorbing unit. Thirty blotters were measured and the area of each blotter calculated. The mean width was 5.59 cm. and the mean height was 5.65 cm. The mean area was 31.57 $cm.^2$, the range was 30.52 to 32.49 $cm.^2$, the standard deviation was ±.52, the standard error .09, the coefficient of variation 1.65.

Variation in thickness of absorbing unit. Thickness of 30 blotters was measured with a micrometer caliper (Brown and Sharpe, No. 11, graduated to .001 mm). The mean thickness was 0.535 mm., the range .52 to .56 mm., the standard deviation ±.01 mm., the standard error ±.002, and the coefficient of variation 1.79.

Time required for weighing. In 20 tests the time required for removing the blotter and making the weighing

averaged 14.5 seconds; an average of 10.0 seconds of this time was required for the balance to reach equilibrium.

Evaporation from the blotter. Some tests demonstrated that each blotter loses a significant part of its moisture if allowed to stand on the balance for 10 minutes and indicate that weighings done with this technique should be done promptly.

Fig. 2 shows that in 1 test more than half of the moisture was lost in 10 minutes. Fig. 3 shows the loss of moisture after 3 different tests and that the curve of evaporation can be charted on a straight line logarithmic function. These measurements suggested that the time (15 seconds) required for weighing did not account for much evaporation. An unused blotter, weighed for 10 minutes under usual weighing conditions, weighed .0008 gm. less at the

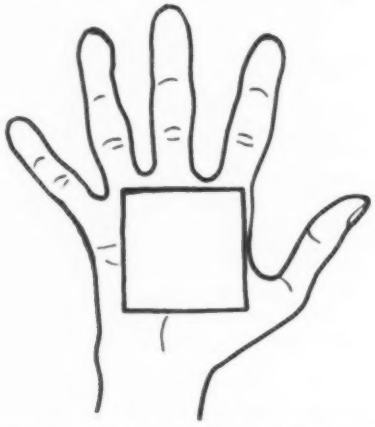

FIG. 1.—Position of the blotter on the right palm, showing that the blotter covers the distal elevations of the palm adjacent to the interdigital clefts.

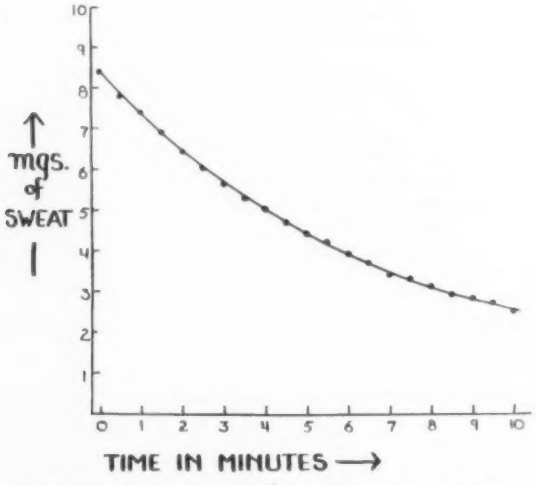

FIG. 2.—Weight of a blotter which after absorbing sweat is weighed every ½ minute for 10 minutes. The 15 seconds required for making the reading is not crucial but too much delay in making the reading would introduce a gross inaccuracy.

end of that period, dropping about .0001 gm. per half-minute period.

Does the examiner's hand add moisture to the blotter? Four different observers were tested to determine if stroking the back or coated side of the blotter added an appreciable amount of moisture to the blotter. No moisture was added, as determined by weighing, when a blotter was placed on a hand encased in a dry rubber glove, the observer stroking the back of the blotter as in the usual test.

This applies only to the experimenters tested. It is possible that some individuals may have finger tips sufficiently moist to introduce moisture even on the coated non-absorbent side.

Testing the possible influence of room conditions (that is, room temperature and relative humidity) on the results of measurements. Table 1 presents data of palmar sweat and room temperature and relative humidity for the 3 groups of subjects studied. Nineteen patients with neurocirculatory asthenia were

TABLE 1.—RESULTS OF INITIAL MEASUREMENTS OF PALMAR SWEAT

33 Patients with Neurocirculatory Asthenia				*74 Healthy Controls*				*30 Healthy Hospital Workers*			
Weight of Palmar Sweat		*Laboratory Conditions*		*Weight of Palmar Sweat*		*Laboratory Conditions*		*Weight of Palmar Sweat*		*Laboratory Conditions*	
R. hand	*L. hand*	*Temp.*	*Humidity*	*R. hand*	*L. hand*	*Temp.*	*Humidity*	*R. hand*	*L. hand*	*Temp.*	*Humidity*
11.8	23.8	85		8.7	10.5	85		11.9	14.0	72	35
5.5	8.5	85		14.3	18.4	—	—	14.4	4.7	73	33
24.5	27.5	85		11.5	10.0	74	47	3.0	6.0	73	33
11.8	25.1	85		12.1	12.5	74	47	6.2	9.5	73	33
20.5	21.0	—	—	15.8	21.0	74	47	10.1	12.5	73	33
36.0	30.5	—	—	18.4	13.7	74	47	4.4	5.2	73	33
24.8	31.0	—	—	17.9	20.9	74	36	4.6	5.1	73	33
28.2	31.8	—	—	9.4	10.6	74	36	4.6	10.0	71	77
17.5	23.0	70	—	19.7	12.9	74	36	9.7	9.5	71	77
17.0	15.0	70	—	9.9	9.0	74	36	7.5	5.1	75	63
23.9	13.3	75	41	42.0	37.4	74	36	3.1	2.1	75	63
14.6	23.0	75	41	11.1	10.9	76	51	4.8	5.3	75	63
15.3	12.2	75	41	23.0	23.1	76	51	7.5	8.6	75	63
58.6	35.5	77	45	20.0	22.7	76	51	13.9	10.1	75	63
18.1	14.6	77	45	16.0	16.0	76	51	3.7	4.4	75	63
25.8	29.1	75	48	11.7	11.4	76	51	11.2	15.5	75	59
12.3	15.7	75	48	21.5	19.8	—	—	2.7	3.8	75	59
12.2	16.8	80	50	16.3	22.6	—	—	11.2	10.9	75	59
6.5	4.7	80	50	20.6	16.5	—	—	10.4	11.6	75	59
13.9	11.3	74	65	39.8	35.4	—	—	10.0	13.4	75	59
4.0	6.4	—	—	37.9	33.9	—	—	10.0	11.3	75	59
10.7	6.2	85	53	30.5	24.6	75	40	10.7	9.3	79	37
9.4	24.4	—	56	31.5	22.8	75	40	22.7	23.5	79	37
15.9	23.5	—	—	31.6	32.7	75	40	17.1	16.3	79	37
28.2	30.6	75	37	5.3	9.2	75	40	5.3	4.8	79	37
25.9	22.7	74	33	27.4	33.0	75	40	9.1	10.4	79	37
21.4	23.3	—	—	10.6	10.0	75	40	28.7	26.7	79	37
36.0	37.3	74	36	24.0	25.0	76	34	3.4	4.2	75	60
9.2	10.3	74	36	11.4	2.4	76	34	3.5	4.2	81	41
29.2	28.9	74	36	17.3	19.3	76	34	8.8	9.2	75	60
7.0	5.0	81	55	8.7	6.9	76	34	—	—	—	—
13.0	10.6	81	55	8.9	9.3	76	34	9.1	9.6	(Mean)	
21.5	14.5	75	50	15.7	17.3	—	—				
—	—	—	—	23.6	17.2	—	—				
19.1	20.5	(Mean)		9.9	11.8	—	—				
				22.9	30.7	—	—				
				17.3	9.3	78	36				
				8.9	13.0	78	36				
				17.5	19.7	78	36				
				14.7	14.2	78	36				
				29.1	25.9	73	46				
				30.2	31.5	73	46				
				10.3	10.3	73	46				
				17.6	14.4	73	46				
				24.0	20.4	73	46				
				16.9	14.5	75	66				
				6.5	6.0	75	66				
				10.1	4.0	75	66				
				10.8	11.5	75	66				
				12.3	10.0	77	45				
				10.0	3.9	77	45				
				14.9	9.0	77	45				
				19.5	13.7	77	45				
				23.8	26.0	77	45				
				—	—	—	—				
				18.0	17.0	(Mean)					

NOTE 1

All palmar sweat weights are in the units: mg./absorbing unit and minute. Laboratory conditions: Temperature is in degrees F., relative humidity is in percentage.

The mean ages of the 3 groups are: patients with neurocirculatory asthenia, 26.8; healthy controls, 23.7; healthy hospital workers, 29.5.

NOTE 2

The values of hand sweat per absorbing unit and minute were not significantly different in patients as compared with comparable healthy control subjects. The mean values of both, however, differed significantly from those of healthy hospital workers. The significance ratios (*i. e.*, the differences between the means divided by the standard error of the differences between those means) are: healthy controls *vs.* patients with neurocirculatory asthenia—right hand .49, left hand 1.61; healthy controls *vs.* healthy hospital workers—right hand 5.22, left hand 4.77; healthy hospital workers *vs.* patients with neurocirculatory asthenia—right hand 4.61, left hand 5.44.

studied with room temperature averaging 76.6°F, with a range of 74 to 85°F. Correlation coefficient between palmar sweat values (mean of right and left hands) and room temperature was −.46. This was not statistically significant[14].

Mean relative humidity for the measurements of this group was 45.53; correlation coefficient between palmar sweat and relative humidity was −.48; this is significant at the .05 level, as compared with .443, and not at the .02 level, as compared with .503[14].

Forty-three healthy control subjects were studied under room conditions with temperature averaging 75.3°F and relative humidity 44.1. The correlation coefficients between palmar sweat and these factors were −.23 and −.18 respectively and are not statistically significant. Thirty healthy hospital workers were studied under room conditions averaging a temperature of 72.5°F and a relative humidity of 50.1. The correlation coefficients between these factors and palmar sweat were +.32 and −.23 respectively and were not significant.

RESULTS FROM TESTS ON PATIENTS AND CONTROL SUBJECTS. *Patients with neurocirculatory asthenia.* Table 1 shows that the mean values of the initial determinations of hand sweat for patients with neurocirculatory asthenia were 19.1 mg. of sweat per absorbing unit and minute for the right hand, and 20.5 mg. for the left hand. Individuals showed, in general, that measurements of the right and left hand were in fair agreement. Statistical constants for this group are in Table 2.

Healthy control subjects. Table 2 shows the values of measurements in 54 healthy control subjects who were brought in for examination, as were members of the neurocirculatory asthenia group. The mean values are 18.0 mg. of sweat per absorbing unit and minute for the right hand and 17.0 for the left hand. The right and left hands showed values at the same level in most cases. Statistical constants for this group are in Table 2.

Healthy hospital control subjects. Table 2 shows the results of measurements in the healthy hospital control subjects. The mean of measurements for the right hand was 9.1 mg. per absorbing unit and minute, 9.6 mg. for the left. Statistical constants for this group are shown in Table 2.

Comparisons between mean values for hand sweat of patients with neurocirculatory asthenia, healthy control subjects and healthy hospital workers. Fig. 4 shows the individual values for palmar sweat of the right hand in patients with neurocirculatory asthenia

TABLE 2. SUMMARY OF RESULTS

DETERMINATION OF PALMAR HAND SWEAT IN RIGHT AND LEFT HANDS OF SUBJECTS WITH NEUROCIRCULATORY ASTHENIA, OF HEALTHY CONTROL SUBJECTS AND OF HEALTHY HOSPITAL WORKERS.

(*Means and calculated statistical constants*)

Group	*No.*	*Means-(mg.)*		*Standard Deviation*		*Standard Error*		*Coefficient of Variation*	
		R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
Neurocirculatory Asthenia	33	19.1	20.5	±10.85	±10.48	±1.89	±1.83	56.80	51.12
Healthy controls	54	18.0	17.0	± 8.55	± 8.63	±1.63	±1.17	49.16	50.76
Healthy hospital workers	30	9.1	9.6	± 5.83	± 5.53	±1.06	±1.01	64.07	57.60

and shows that the mean of these values is almost the same as that of the healthy control subjects. The slight difference is not statistically significant, significance ratio .49. In contrast, both the neurocirculatory asthenia group and the healthy control group show significantly higher means than that of the hospital control group—significance ratios were 4.61 and 5.22 respectively.

The same type of results was obtained in measurements of the left hand, that is (Table 1) the neurocirculatory asthenia patients and the healthy controls showed means which are not significantly different (significance ratio 1.61), while they both differ from the healthy hospital control group (significance ratios being 5.44 and 4.77 respectively.)

This suggests that the patients and controls from outside the hospital showed moist palms in the initial test while the workers accustomed to the hospital and its procedures did not.

Comparison of amounts of palmar sweat of the right and left hands. Table 1 presents the data for measurements of right and left hands for each patient. In 33 patients with neurocirculatory asthenia the mean of the right hand is 19.1 mg. per absorbing unit and minute, for the left 20.5. The difference between the mean of the right and left hand measurements is not statistically significant; the standard error of this difference was ± 1.5, the significance ratio was .93. There was an obvious correlation between the right and left hand sweat values, correlation coefficient .767, which was statistically significant, significance ratio 5.5.

In 54 healthy control subjects, the mean value for the right hand was 18.0 mg. of sweat per absorbing unit and minute, for the left hand 17.0. This difference was not significant, as the standard error of this difference was .54, the significance ratio was 1.85. The correlation coefficient between individual right and left hand values was .892, which was statistically significant; significance ratio was 10.2.

In 30 healthy hospital workers, the palmar sweat of the right hand was 9.1 mg. per absorbing unit and minute, for the left hand 9.6; this difference (Table 2) was not statistically significant, the standard error of this difference was ± 0.49, the significance ratio 1.2. The correlation coefficient between palmar sweat of right and left hands was .908, which was significant; significance ratio was 7.9.

The difference between the differences of right and left hand sweat were not significant (significance ratios were: neurocirculatory asthenia *vs.* healthy controls, 1.5; neurocirculatory asthenia *vs.* healthy hospital workers, .60; healthy controls *vs.* healthy hospital workers, .69.)

These data and calculations show that there was no difference in the means of right and left hand palmar sweat values for right and left hands in each group, that the individual values for right and left hand palmar sweat were highly correlated, and that the differences between values of right and left palmar sweat of one group do not significantly differ from those differences in the other groups.

Measurements of hand sweat in other conditions and under varying circumstances. This section will report on some observations that are related to the possible usefulness of the method in other conditions and under varying circumstances.

Twelve cases of thyrotoxicosis were studied. They showed a mean value of 21.4 mg. of sweat per absorbing unit and minute for the right hand, 22.2 mg. for the left.

A patient with hyperhydrosis showed values of 60.8 mg. per absorbing unit and minute for the right hand, 53.1 mg. for the left hand. A second study

on this patient showed values in the right hand of 53.0 mg., in the left hand of 57.5 mg.

A patient who had had right sympathetic ganglion denervation a year before showed a value of 5.1 mg. per absorbing unit and minute in the right hand, in contrast to 23.5 mg. in the left hand.

Two patients and 2 control subjects had measurements made over a 9-day period. Table 3 shows that the values decline for each patient during this period, but that the highest subject remains highest and the lowest remains lowest.

Table 1 lists room temperature and room relative humidity along with values of palmar sweat for different patients. Fig. 5 shows palmar sweat values in one individual studied under varying conditions of room temperature and room humidity. There is no related change of palmar sweat to match the rising room temperature and rising relative humidity as charted in this figure.

These data suggest that if the room temperature and room relative humidity are factors which influence palmar moisture, their effect is not an obvious or strongly determining one under usual conditions. Results of observations on the possible relations of other factors to palmar moisture will not be described in this report.

Discussion and Speculation. This report describes a simple method for

TABLE 3.—VALUES OF PALMAR SWEAT IN A 9 DAY PERIOD

Palmar Sweat—mg. absorbing unit and minute

	Patient I		*Patient II*		*Control I*		*Control II*	
Day	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1	28.2	30.6	22.7	25.9	17.7	18.0	5.7	5.2
5	31.9	31.5	24.4	23.7	7.8	7.5	4.6	5.3
7	21.1	21.9	23.0	21.9	10.3	16.6	7.2	7.4
8	31.4	29.3	19.0	20.7				
9	15.4	20.6	12.3	11.9	6.8	6.2	5.0	4.7

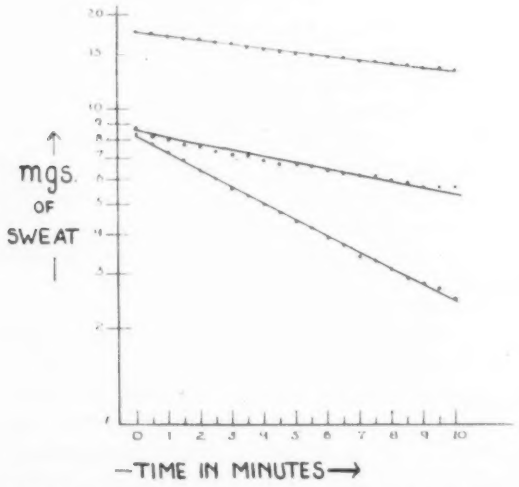

FIG. 3.—The evaporation of moisture from blotters in 3 different tests. The diminishing weights are plotted on a logarithmic scale, and when so plotted the curve approximates a straight line.

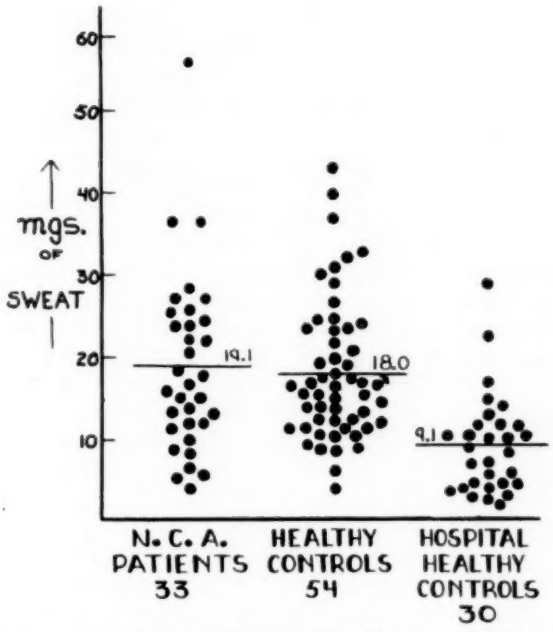

FIG. 4.—Patients with neurocirculatory asthenia and healthy control subjects who are outsiders to the hospital environment do not differ significantly from each other in amount of hand sweat when tested in the laboratory, but both groups differ significantly in their initial tests. in amount of hand sweat from healthy control subjects who are accustomed to the hospital and laboratory environment.

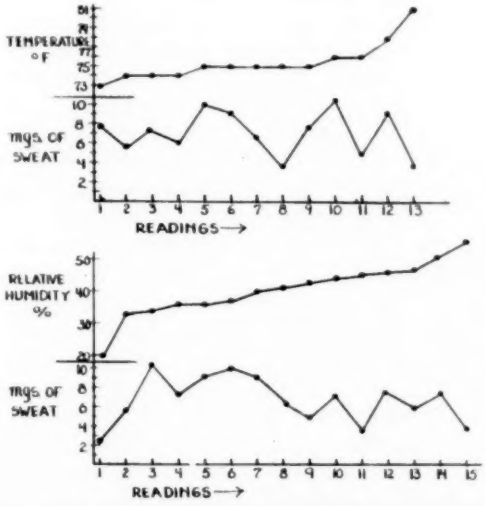

FIG. 5.—The palmar sweat of 1 individual under varying environmental conditions of room temperature and relative humidity. There is no obvious relation between amount of palmar sweat and either the temperature or the relative humidity of the laboratory.

measuring amounts of sweat over various portions of the skin and its specific use in measuring palmar sweat. It should be pointed out that this technique, as described here, has certain limitations and certain advantages. Some of the obvious limitations are as follows: The determinations were done in the laboratory since no method had been developed to allow for transportation of the blotters to the laboratory without evaporation, and transporting a sensitive balance of the type used was somewhat impractical. As yet no studies have been made which show precisely what is absorbed or what proportion of that which might be absorbed is actually absorbed. Until such studies are done in detail the method depends on the assumptions that the moisture absorbed is for the most part sweat and that the absorbing unit takes up a significant and fairly regular amount of that sweat which is present. The test as described here did not attempt to differentiate the sweat which was on the hand at the beginning of the test from that which was formed during the minute when the blotter was applied. The possible influences of environmental factors such as effect of room temperature, relative humidity, rest period before test, food before test, effects of washing and drying hands had not been worked out completely at the time these studies were made; and obviously such knowledge is necessary if studies from different laboratories are to be compared. For the purpose of the determinations made in the patients here it was desired to have no special preparation for the test.

The purpose of this study was not, it should be emphasized, to describe the physiology of palmar sweat but to provide a technique for measuring the phenomenon that clinicians describe as "moist palms." The advantages of the method are that it is simple, quantitative, takes very little time, uses an instrument of precision for the measurement, and, finally, measures *directly* what the investigator wishes to measure, that is, the clinical phenomenon of moist palms. Also, amounts of sweat from other parts of the body, such as sole of the foot or forehead may be measured by this method.

It is of historical interest that using filter paper as an absorbing unit for sweat was described in animal experimentation[16] and was described as "laborious and subject to so large an experimental error that it cannot be used to detect differences not immediately obvious to the naked eye"[2]. It is believed that the method described here is not laborious and that it can quantitate a phenomenon objectively which cannot be quantitated but can be estimated with a reasonable degree of accuracy by a careful clinician. For instance, one of the great observers of all time[13] wrote:

"But oh, what a clammy hand his was! as ghostly to the touch as to the sight! I rubbed mine afterwards, to warm it, *and to rub his off*.

"It was such an uncomfortable hand, that, when I went to my room, it was still cold and wet upon my memory."

And further:

"I found Uriah reading a great fat book, with such demonstrative attention, that his lank fore-finger followed up every line as he read, and made clammy tracks along the page (or so I fully believed) like a snail."

Other simple methods for detecting small amounts of sweat have been those that depend on adding a substance to the skin which changes color in the presence of moisture[15,27] or using a specially prepared paper which changes color in the presence of sweat[33]. These methods are simple and useful; they are not, for the purpose described in this report, quantitative or direct measurements of amounts of sweat. Other methods have regarded

"palmar galvanic skin reflex" as synonymous with "palmar secretory activity" without the necessary crucial data to show that one is, in fact, a quantitative measure of the other[11,12] as the terminology, based on assumption and little actual correlated observation, implies. It is not clear, as yet, whether this assumption is true or not,[19,26,31]. Quantitative methods applicable to measuring the amount of small amounts of sweat[19] and for the chemical analysis of small amounts of sweat have been described[24,25] and are applicable for securing more detailed and precise chemical information.

The data show here that the first test of the amount of palmar moisture in patients with neurocirculatory asthenia revealed no excess of palmar moisture when they were compared with comparable healthy control subjects who were also strangers to the laboratory and to the hospital environment. This suggests that the discovery of moist palms at first physical examination cannot be used as a useful feature of diagnosis in neurocirculatory asthenia. This may imply a contradiction with other observers[1,9,10,20,28,33,34], but it should be emphasized that these authors presented either impressions with no data or clinical data which showed that some patients with neurocirculatory asthenia had moist palms but did not present data on comparable control subjects. It is of interest that from observations[5] made at the selective service board on 100 selectees of various clinical manifestations including palmar sweat, it was concluded that excessive palmar sweat was practically universal under those circumstances and occurred in healthy men as well as in men with "neurosis". This corresponds with a popular belief that moist palms may be present during students' oral examination, interviews for jobs, or under other circumstances, such as during examination by a physician, without signifying neurocirculatory asthenia, anxiety neurosis, neurasthenia, or effort syndrome.

Nothing was learned in this study about the purpose of "palmar sweat." It has been alleged that its purpose is to prepare for muscular activity[19] or other "aspects of adaptive behavior"[12]. In the absence of verbal communication from the sweat glands about their purpose it seems well to rely on observations and to omit unfounded speculations, no matter how plausible.

Routine clinical examinations on a series of patients with neurocirculatory asthenia[6] revealed that 57.7% of 71 patients with chronic neurocirculatory asthenia had excessively moist palms in contrast to 42.8% of 56 healthy control subjects. This difference in proportion was not significant; significance ratio was 1.7. Sweaty axilla was recorded in 37% of 72 patients with chronic neurocirculatory asthenia, as compared with 15% of 55 healthy control subjects. This difference in proportions was significant, and the significance ratio was 2.95 A study that does not take up neurocirculatory asthenia and anxiety neurosis as such[32] reports on the presence of excessive palmar sweat, using a color technique. It states that in general more hospitalized neuropsychiatric cases showed an "intense response" of palmar sweat than did other patients or hospital personnel. In addition, 83% of all 1160 hospital patients showed a "strong" or "intense response"; 84% of 100 "neuropsychiatric patients" showed the same. This was in contrast to 32% of 71 hospital workers who showed the "strong" or "intense" response, and indicates a contrast between general and neuropsychiatric patients considered as a group on the one hand, and hospital workers as the other group. Certain similarities between those data and the observa-

tions and conclusions of this study are suggested.

It is quite possible that on repeated tests the patients of this study might show differences as compared with healthy control subjects, or that patients might consistently show higher values while the control subjects returned to normal limits, or that the patients' reactions to various stimuli or situations might be excessive. No data, however, are reported here that prove or disprove such possibilities, the emphasis of this report being upon the first test of each subject.

Finally, the use of a simple test of this sort in psychological tests as an indicator of "stress" or as a useful tool in clinical neurology is to be considered.

Conclusions. 1. The technique of measuring palmar sweat by use of a blotter and sensitive damped analytical balance is simple, direct and useful.

2. The values of palmar sweat of right hand and left hand for individuals were highly correlated, and there was no significant difference between the means of measurements of right and left hand.

3. Measurements of palmar sweat by this technique show that on first examination 33 patients with neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome) have measurements (right hand: 19.1 mg. of moisture per absorbing unit and minute; left hand: 20.5) that do not differ significantly from those of 54 comparable healthy control subjects (right hand: 18.0; left hand: 17.0).

4. These groups both differ in this respect from 30 healthy hospital control subjects, who show significantly lower amounts of palmar sweat (right hand: 9.1; left hand: 9.6).

5. The observation of "moist palms" is not a reliable diagnostic sign of neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome).

6. It is concluded that environmental factors such as familiarity with the surroundings and the procedure may materially affect palmar sweat.

7. It is believed that the simple technique described for quantitating amounts of skin sweat may be useful in psychological and neurological studies.

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THE EFFECT OF AUREOMYCIN ON CERTAIN LIVER FUNCTION TESTS AND BLOOD COAGULATION*

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That aureomycin may alter certain liver function tests was suggested by the laboratory findings in a patient who was receiving the drug empirically during a febrile illness of undetermined etiology.

While receiving 2 gm. per day of aureomycin in 4 doses of 0.5 gm. each, the course of the illness indicated the need of liver function tests. The results of the determination of stool urobilinogen, urine bile, and serum bilirubin were incompatible in the well established concepts of bile pigment formation, transport, and excretion. The stool was negative for urobilinogen, urobilinogen was present in the urine but not increased, serum bilirubin was 0.3 mg. p. 100 ml., and urine bilirubin was negative. The cephalin flocculation test was 4+.

As the persistent absence of urobilinogen from the stool would imply exclusion of bilirubin from the gut by extra hepatic obstruction, this experiment was done to determine whether or not the use of aureomycin could be responsible for the unusual laboratory findings.

Procedure. Accordingly, aureomycin was administered to 5 healthy adult males, the oral dose being 500 mg. before each meal, and 500 mg. at bedtime for a total of 2 gm. per day, for at least 7 days, and in some cases for 10 days.

As a report[4] of aureomycin shortening clotting time has appeared in the literature advantage was taken of our unusual opportunity to study clotting time and prothrombin time.

Each morning the following determinations were done on each of the subjects: 1, Stool urobilinogen by the Sparkman[5] method; 2, Urine urobilinogen by the Wallace-Diamond[6] technique; 3, Stool bilirubin—qualitative technique; 4, Urine bilirubin—Gmelin's method; 5, Serum bilirubin—direct reacting and indirect reacting; 6, Cephalin flocculation test of Hanger; 7, Clotting time by Lee-White method; 8, Prothrombin percentage by Owren method.

Two days of controls were established before the administration of the drug was begun.

Results. 1. Stool urobilinogen: all stools in the control period registered amounts within the normal range. After 3 days of receiving aureomycin the stools of 4 subjects contained no urobilinogen. After 4 days, the reading was zero on the stools of all 5 subjects. all stools remained negative for urobilinogen throughout the remainder of the period of administration of the drug, and for at least 2 days after cessation of medication. Specimens from 2 of the 5 were negative for a known 3 days after cessation of aureomycin.

* Aureomycin was generously supplied by Dr. Stanton M. Hardy of the Lederle Laboratories, Pearl River, New York.

2, Urine urobilinogen remained at control levels (1:10-1:20) throughout the duration of the experiment. 3, Stool bilirubin was determined qualitatively only. All stools were negative during the control period. In each individual this test became positive at the time that the stool urobilinogen became negative. This inverse relationship of stool bilirubin—urobilinogen persisted throughout the experiment. 4, Urine bilirubin: at no time during the control period nor during the phase of medication was bilirubin found in any urine samples. 5, Serum bilirubin: Direct reacting serum bilirubin was negative for all specimens from all subjects. Indirect reacting serum bilirubin showed minor fluctuations in all subjects, but no abnormal or significant changes. 6, Cephalin flocculation tests were all negative in all subjects during both periods of the study. 7, Clotting time determination by the 3 tube Lee-White method using ordinary glass tubes revealed a prolongation above that of the control period of the average clotting time in 4 of the 5 subjects. The clotting times, measured to the nearest 30 second intervals averaged during the control period and treatment period respectively in minutes were: 9.25 and 15.5; 9.5 and 12.5; 10.7 and 17.7; 15.5 and 21.3; 16.5 and 16.5. 8, Daily prothrombin percentages exhibited somewhat inordinate variations. Little significance is attributed to them at this time, although they will not be dismissed without further evaluation.

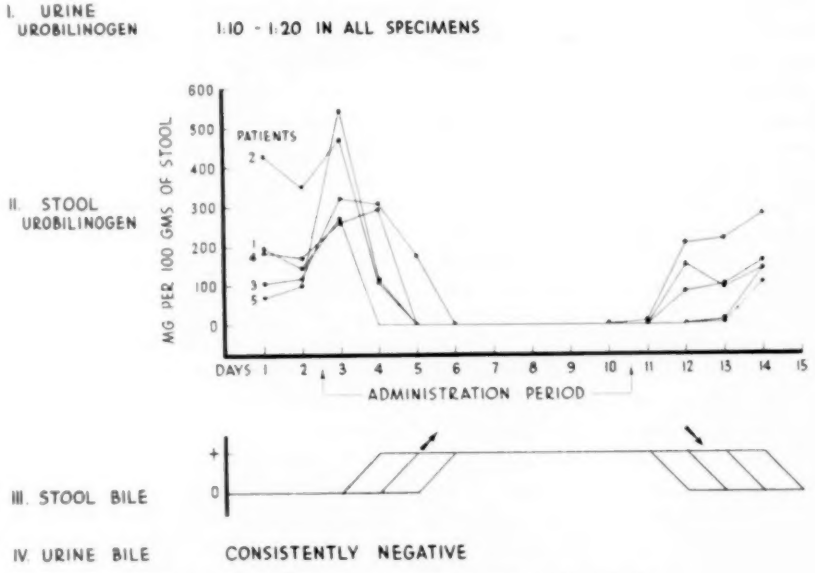

FIG. 1—The Effect of Aureomycin: ON I, II, III, IV

Discussion. Aureomycin alters the fecal content of urobilinogen in healthy adult males. It is believed that this is achieved by its action in preventing the conversion of bilirubin to urobilinogen in the intestinal tract. It has been noted in this regard that sulfaguanadine exerts a similar but not nearly so marked a depression on fecal urobilinogen[2].

It is suggested that as well as any specific sensitivity of the supposed bacteria involved in urobilinogen

metabolism, there is the additional factor of appreciable re-excretion of aureomycin back into gut via the biliary passages[3]. Dearing and Heilman have evaluated a wide range of chemotherapeutic and antibiotic agents, and have found aureomycin to be the most effective of all in removing bacteria from the intestinal tract. In spite of this, serum and urine bile pigment studies remained normal in this series of 5 subjects.

It was not anticipated that urobilinogen would persist in the urine after its formation in the gut had been stopped for a number of days. We must therefore consider that 1 of 3 processes has occurred: either the Sparkman[5] technique does not detect minute amounts of stool urobilinogen; the Wallace-Diamond[6] may give falsely positive urine urobilinogen determinations, or previously reabsorbed urobilinogen is very slowly excreted, giving a positive urine test for an undetermined number of days after production has stopped.

No evidence was found that bilirubin is reabsorbed from the gut. When the fecal level was known to be increased, there was no rise in serum bilirubin nor did urine bilirubin appear. The normal clearing of bilirubin and urobilinogen by the liver, plus the normal cephalin flocculation tests indicate that aureomycin exerts no toxic effects on the liver as evaluated by these techniques.

The results of this experiment caution us that the indiscriminate use of aureomycin could add to the difficulties in the differential diagnosis of the cause of jaundice, and of hepatitis without jaundice.

The inherent limitations of the routine Lee-White method of determining coagulation time are well publicized. However, the prolongation of the coagulation times of 4 of the 5 subjects should be seriously considered. This prolongation is at variance with the reported findings of Macht and Farkas.

Conclusions. 1. Aureomycin in a dosage of 2 gm. per day in healthy adult males will eliminate urobilinogen from the stool and cause a rise in stool bilirubin.*

2. Small amounts of urobilinogen persist in the urine when none can be found in the stools.

3. Serum bilirubin, direct or indirect, is unchanged with the above findings.

4. Cephalin flocculation tests are unaltered.

5. Clotting time by the Lee-White method is prolonged in 4 of 5 cases.

6. Prothrombin percentage does not show a consistent or significant change.

* Similar studies are under way using Chloramphenicol (Chloromycetin).

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SPIROMETRY AS A MEANS FOR STUDYING VENTILATORY FUNCTION OF PATIENTS IN MECHANICAL RESPIRATORS

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Respiratory inadequacy is an important consideration in a wide variety of disorders. Although most notable perhaps is acute poliomyelitis, there are many conditions such as myasthenia gravis, acute porphyria, Guillain-Barré syndrome, narcotic and barbiturate poisoning, diphtheria, and spinal cord injuries[1] in which respiratory dysfunction is the prime consideration and constitutes the principal cause of death. Respiratory dysfunction is of 2 main types, namely alveolar and ventilatory deficiencies. This classification was used by Cournand and Richards[2], Ornstein *et al.*[19], and recently by Elam and his co-workers[7,8]. *Alveolar deficiency* indicates the faulty transport of gases across the alveolar membrane, and *ventilatory deficiency* the inadequate movement of gases into and out of the lungs.

Elam and his collaborators have shown in studies with oximetry in poliomyelitis that both types of pulmonary deficiency can occur either singly or together. The alveolar deficiency can be due to: 1, pulmonary edema, 2, atelectasis, or 3, pneumonia; and the ventilatory deficiency to 1, paralysis of the diaphragm and, or, intercostal muscles, 2, depression of the respiratory center, or 3, obstruction of the upper airway[11]. In this report, *peripheral* ventilatory deficiency will be used to indicate paralysis of the respiratory musculature, and *central* ventilatory deficiency to indicate damage of the respiratory center.

The dangers of anoxia or hypoxia are logically combatted by the use of oxygen, bronchoscopy, tracheotomy or intubation, and by artificial respiration. Since mechanically supported respiration is so frequently required, it seems strange that although much has been written on the care of respirator patients[1,6,10,13,21-23,26-30], there has been only one definitive clinical study[7,11], of ventilation in respirator management.

The spirometer has been used by a number of investigators[2-5,15-19,25] in the study of emphysema, heart failure, and tuberculosis in order to estimate ventilatory function and reserve. It also has been employed to determine the effects of various forms of collapse therapy. Elam[11] was the first to report the use of this apparatus in poliomyelitis but his patients were in the convalescent phase of the disease.

There are 4 problems to consider when ventilatory dysfunction develops: 1, optimal time for respirator placement, 2, selection of suitable negative pressures, 3, downward ad-

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justment of negative pressures during recovery of respiratory function, and 4, optimal time for removal from the respirator. It is the purpose of this communication to demonstrate that spirometry can assist in the solution of these problems.

Material, Equipment, and Methods. *Material.* Five patients with some type of ventilatory deficiency were used in this study. Four were admitted to the poliomyelitis unit of the University of Texas Hospital during the summers of 1948 and 1949, and 3 of these required the support of a mechanical respirator. The 5th was a young man suffering from a cervical spinal cord injury.

Equipment. The spirometer used was a Sanborn waterless basal metabolism apparatus, the important features of which were: 1, double breathing tubes with large inside diameters to reduce resistance; 2, a 4 liter bellows-type air chamber connected by chain and pulley to a recording stylus; 3, waxed recording paper mounted on a motor-driven kymograph. An oronasal mask fitted to the face by an inflatable cuff replaced the usual rubber mouthpiece employed in basal metabolism tests. In those patients with a tracheotomy, a soft rubber sleeve was used to connect the spirometer and the tracheotomy cannula. Cournand *et al.*[4] stated that this type of spirometer is not ideal because of the inertia and resistance in its different parts. They pointed out, however, that for practical purposes the limitations are of minor importance. The widespread availability of this or a similar basal metabolism machine seemed to justify its use in this study.

The respirators used were of two types. One was the standard Emerson cabinet-type machine; the other was a portable chest-type respirator.

The spirometer was calibrated by introducing a known amount of gas into the air chamber and measuring the excursion of the stylus. Once this had been accomplished for a particular machine, the calibration remained constant.

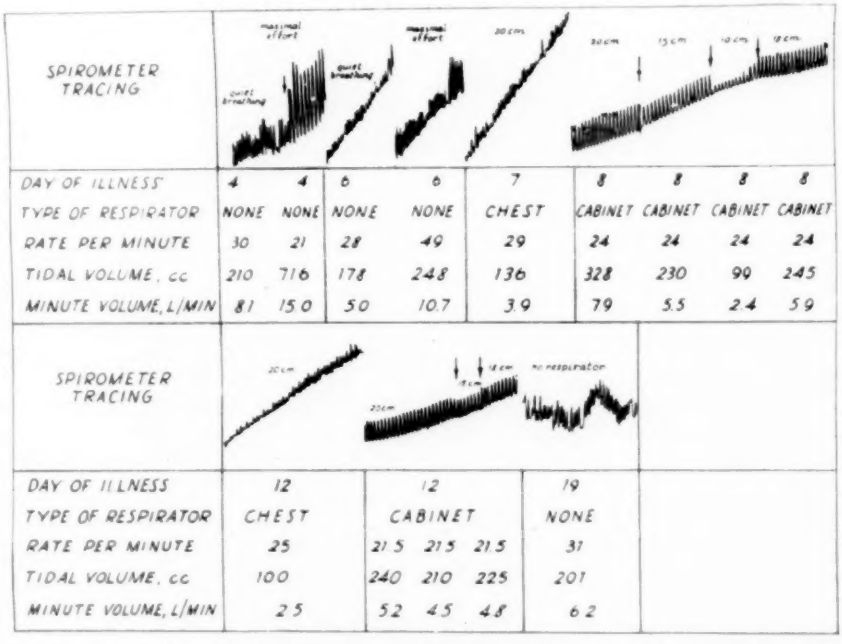
In order to avoid undue apprehension, whenever possible the procedure of making spirometric tracings was explained to the patient and assurance of its harmlessness given. Oxygen was used routinely in all our measurements although in the determination of respiratory minute volumes the gas chamber can be filled with either air or oxygen[16]. The mask was applied tightly to the face and checked for leaks before the tracing was made. In patients with a tracheotomy, the soft rubber sleeve previously mentioned was attached to the removable inner cannula of the tracheotomy tube. The cannula was then replaced in its usual position and during the tracing special precautions were observed to prevent air leakage through the nose and mouth. This was accomplished either by holding the nose and mouth, or placing a closed mask over the face.

Calculation of the minute volume in cubic centimeters was made by multiplying the average tidal volume of inspiration in cubic centimeters by the number of respirations per minute (Min. Vol.=Av. Tidal Vol. × Rate). This value was judged as to adequacy by comparing it with the normal minute volume for that patient. For the purposes of this study, "normals" for minute volume of respiration were calculated from a formula devised by Swann[24]. This formula, Min. Vol.$=0.292 \times \text{Wt.}^{0.75}$, requires the assumption that 7.0 liters per min. is the normal resting minute volume for a 70 Kg. person. Examples of minute volumes so determined are: 7.0 liters per min. for a 70 Kg. individual, 5.5 liters per min. for one weighing 50 Kg., and 2.8 liters per min. for a 20 Kg. child. In the patient in whom spirometry was used before the development of ventilatory embarrassment, the "normal" value so obtained served as an adequate standard.

Results. The experimental data are presented in conjunction with the clinical description of the patient's condition during the course of study.

Case 1. V. M., a 38 year old housewife entered the poliomyelitis unit on the 3rd day of an illness beginning with fever, headache, nausea, vomiting, and aching in the back and shoulders. At entry neck and back stiffness, muscle fasciculations, and bilateral lower extremity weakness were demonstrable. Cerebrospinal fluid findings were consistent with a diagnosis of acute poliomyelitis. Clinical evidence of respiratory muscle weakness developed on the 4th day of illness. Spirometric tracings (Fig. 1) showed a slight degree of hyperventilation on quiet breathing (8.1 l. per min.), but there was a marked decrease in ventilatory reserve. By the 6th day, paralysis had increased in the lower extremities and respiratory muscles and had appeared in the upper extremities and abdominal musculature. Spirometry at this time revealed an almost normal resting minute volume (5.0 l. per. min.) but a greater decrease in ventilatory reserve. Because of a further decrease in the minute volume, placement in a respirator was effected. The

patient's condition then remained satisfactory until the 8th day when she developed a partial upper respiratory obstruction due to pharyngeal paralysis. In spite of the assistance of the chest-type respirator operating at a fairly high negative pressure (20 cm. of water), an adequate minute volume was not being provided (3.9 l. per min.). Consequently, endotracheal intubation was performed and the patient transferred to a cabinet-type respirator. Spirometry now showed that ventilation was adequate (5.9 l. per min.) at a negative pressure of 18 cm. Following removal to the standard respirator, adequate minute volume (5.2 l. per min.) was obtained at a negative pressure of 20 cm. of water. During the following 7 days the central and peripheral ventilatory deficiencies improved markedly and on the 19th day the patient was found to be capable of supporting her own respiration (minute volume of 6.2 l.). On the 28th day she was able to dispense with the artificial airway and showed subsequent increase in function of all musculature. Convalescence was gradual but uncomplicated by further respiratory difficulty.



DAY OF ILLNESS	4	4	6	6	7	8	8	8	8
TYPE OF RESPIRATOR	NONE	NONE	NONE	NONE	CHEST	CABINET	CABINET	CABINET	CABINET
RATE PER MINUTE	30	21	28	49	29	24	24	24	24
TIDAL VOLUME, cc	210	716	178	248	136	328	230	90	245
MINUTE VOLUME, L/MIN	8.1	15.0	5.0	10.7	3.9	7.9	5.5	2.4	5.9

DAY OF ILLNESS	12	12			19	
TYPE OF RESPIRATOR	CHEST	CABINET			NONE	
RATE PER MINUTE	25	21.5	21.5	21.5	31	
TIDAL VOLUME, cc	100	240	210	225	201	
MINUTE VOLUME, L/MIN	2.5	5.2	4.5	4.8	6.2	

FIG. 1. CASE 2.—Spirometric tracings (reduced to ⅔ actual size) of a 37 year old woman with ventilatory deficiency due to bulbo-spinal poliomyelitis. Endotracheal intubation and tracheotomy performed on the 8th and 12th days respectively. Negative pressure values in centimeters of water are indicated above the tracings.

of water. Subsequent determinations of the minute volume were made daily in order to determine the proper negative pressure. She continued to do well until the 12th day when, because of pharyngeal ulceration and the continuing need for an artificial airway, a tracheotomy was performed. At this time it became apparent that central ventilatory failure was developing. The inadequacy of the portable chest respirator in the presence of central failure was demonstrated by spirometry (12th day in Fig. 1) even though this was not immediately apparent clinically.

Comment on Case 1. Severe obstructive ventilatory deficiency as well as moderate peripheral and central respiratory impairment were demonstrable in this patient. The course of the ventilatory difficulties can be followed in Fig. 1. Spirometry had its greatest value in this patient in determining the negative pressures which would afford adequate ventilation but still not

cause hyperventilation. This patient weighed 52 Kg., and normal resting minute volume was estimated to be 5.5 l. per min. The tracings obtained on the 8th and the 12th days reveal the different negative pressures which were required to provide comparable ventilation. Cognizance of and adjustment for this day to day variation would not have been possible without the aid of spirometry.

The indications for respirator placement based on clinical perception alone are inaccurate. Spirometry proved of inestimable value by providing an objective and easily repeatable measurement of ventilatory adequacy. The worth of the procedure was demonstrated not only in determining the initial need for artificial respiration on the 6th day, but also in recognizing the inadequacy of the chest respirator on the 7th and 12th days. It is of interest to note that in this patient the chest respirator was unable to provide adequate ventilation (12th day) at negative pressures which were adequate in the cabinet respirator.

A 3rd application of spirometry was in following the progression of peripheral respiratory involvement by determination of the ventilatory reserve. This is exemplified in the tracings of the 4th and 6th days where the reserves respectively were 270% and 195% of the resting value, as compared with the 1300% expected in a normal adult female[19]. Furthermore, the record of the 6th day clearly indicates that an increase in respiratory rate rather than an increase in tidal volume was primarily responsible for even the small reserve that remained.

Finally, spirometry as an index of the increasing ventilatory function during the patient's convalescence, afforded an objective criterion for the early discontinuance of artificial respiration.

Case 2. F. H., a 6 year old white girl was admitted to the otolaryngology service on the 5th day of an illness beginning with fever and headache. Difficulty in swallowing and talking developed on the 2nd day and episodes of choking became manifest on the 3rd day. At the time of entry, the only findings were dysphagia and dysphonia. Cerebrospinal fluid examination corroborated the diagnosis of bulbar poliomyelitis. During the succeeding 4 days, the patient developed a slight degree of weakness in the lower extremities, neck, and respiratory musculature. By the 9th day she was apparently over the acute stage of the illness and was doing well. On the 11th day, however, she developed increasing difficulty in swallowing, which resulted in respiratory obstruction. A spirometric tracing at that time showed a deficient respiratory minute volume (1.6 l. per min.). She was then placed in a chest-type respirator, but in the presence of continued respiratory obstruction, even very high negative pressures (34 cm. of water) were ineffective (Fig. 2). Following a tracheotomy, it became apparent that central ventilatory failure had developed. The spontaneous respiratory rate was only 2 per min. (Fig. 3) and the minute volume was only 0.15 l. per min. (Fig. 2). Following placement in a cabinet-type respirator, adequate ventilation (4.0 l. per min.) was provided by a negative pressure of 20 cm. of water. During the following days, there was gradual improvement of central ventilatory function. On the 12th day, the spontaneous respiratory rate had risen to 8 per minute although the minute volume was still very low (Fig. 2). By the 15th day the spontaneous rate had risen to 27 per minute and the minute volume to 3.8 l. However, because of considerable irregularity in breathing she was kept in the respirator, maintaining adequate ventilation (4.5 l. per min.) at a reduced negative pressure (10 cm. of water). By the 17th day, breathing had become regular and spontaneous ventilation was 3.4 l. per minute with a rate of 22 per min. Hence, she was removed from the respirator. Subsequent recovery was uneventful.

Comment on Case 2. This patient showed central ventilatory deficiency in addition to marked obstructive ventilatory deficiency. The results of minute volume tracings are shown diagrammatically in Fig. 2. As in the previous patient, spirometry was of value: 1, in determining the necessity of respirator placement; 2, in choosing proper respirator pressures; and 3, in

demonstrating the ability to support spontaneous respiration.

It is of interest that at various times widely differing negative pressures were required to give the ventilation (3.5 l. per min.) considered to be normal for this 18 Kg. child. In general her condition was reflected in these pressures, *e.g.*, 20 cm. of water on the 11th day, 25 cm. on the 12th day, 15 cm. on the 14th, and 10 cm. on the 15th day. This rapid change from day

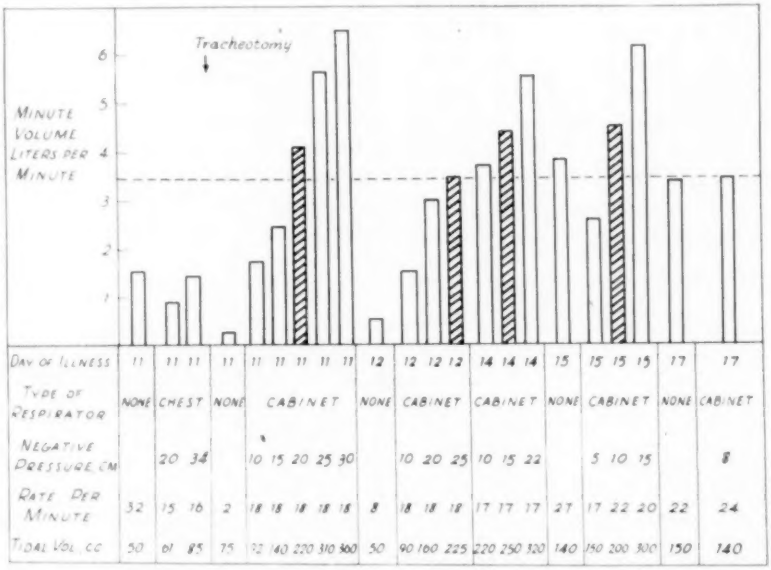


FIG. 2. CASE 2.—Bar graph of minute volumes of a 6 year old girl with ventilatory deficiency due to bulbar poliomyelitis. The dotted line at minute volume of 3.5 l. represents the estimated normal for this patient. The cross-hatched bars indicate the negative pressure settings which were used on various days following evaluation by spirometry. Tracheotomy was performed on the 11th day.

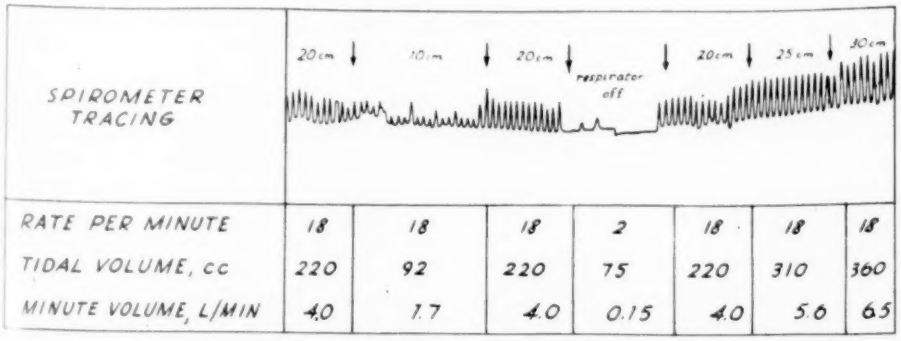


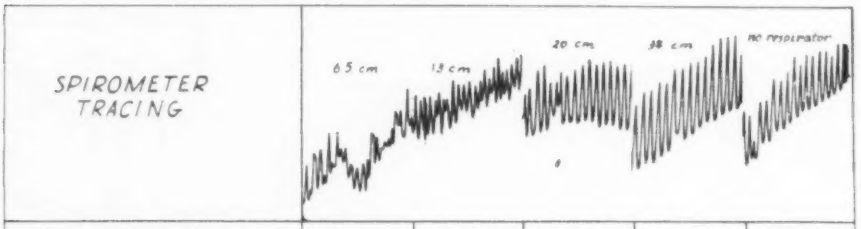
FIG. 3. CASE 2.—Spirometric tracing (reduced to 7/10 actual size) obtained on 11th day of illness following onset of central ventilatory failure. At this time she had a tracheotomy and was in a cabinet-type respirator. Negative pressure in centimeters of water is indicated above the tracing. The period of apnea evident when the respirator is off is characteristic of central failure, and the tracing following this demonstrates the effectiveness of the respirator in providing effective ventilation.

to day was more evident in this patient whose primary difficulty was central than in a patient (Case 5) with peripheral deficiency.

In these 2 patients (Cases 1 and 2) who had central ventilatory failure, the cabinet-type respirator proved very effective (Fig. 3), once obstruction of the airway had been relieved. These data indicate the fallacy of the widespread belief that the respirator is contraindicated in the presence of central failure. Perhaps the reason for this erroneous concept lies in the frequent association of obstructive with central ventilatory deficiency. Such a situation is illustrated by the graph of ventilatory volumes preceding the tracheotomy on the 11th day (Fig. 2). In this instance negative pressures as high as 34 cm. of water were ineffective.

CASE 3. S. M., a 14 year old Latin-American boy was admitted to the orthopedic service* with a fracture-dislocation of the 4th cervical vertebra following a dive into shallow water. Almost complete dysfunction of the spinal cord existed below this level. The patient therefore had paralysis of the thoracic and abdominal musculature, but adequate function of the diaphragms. Because of subjective respiratory distress on the 2nd day he was placed in a portable chest respirator with negative pressures of 13 to 15 cm. of water. On the 3rd day, the pediatric service was consulted regarding the management of the respirator at which time spirometric tracings (Fig. 4) revealed that ventilation was adequate without the respirator (7.3 l. per min.) Artificial respiration therefore was discontinued and with reassurance by the attendants, the patient evinced no further need of the respirator.

Comment on Case 3. Peripheral ventilatory deficiency of mild degree due to paralysis of the thoracic musculature is well shown in this case study. It was because of subjective respiratory distress that respirator placement had been effected. Spirometry demonstrated that the respirator was not only unnecessary but actually detrimental. The negative pressures at which the machine had been operating (13 to 15 cm. of water) actually reduced ventilation (Fig. 4) to below the estimated normal of 6.5 l. per min. expected in this 60 Kg. boy.



TYPE OF RESPIRATOR	CHEST	CHEST	CHEST	CHEST	NONE
RATE PER MINUTE	25	24	17	15	18
TIDAL VOLUME, cc	180	216	390	550	405
MINUTE VOLUME, L/MIN	4.5	5.2	6.6	8.3	7.3

FIG. 4. CASE 3.—Spirometric tracings (reduced to 8/10 actual size) of a 14 year old boy with ventilatory deficiency due to a cervical spinal cord injury. Negative pressure in centimeters of water is indicated above tracings. Adequacy of ventilation without the respirator is apparent.

CASE 4. C. B., a 28 year old physician entered the poliomyelitis unit on the 2nd day

* Acknowledgment is made to the Department of Orthopedics for permission to report this case.

of an illness beginning with fever, severe headache, and pain in the back. At entry fever and stiffness of the back were noted. Cerebrospinal fluid findings were consistent with a diagnosis of acute poliomyelitis. During the following 4 days paresis developed in all extremities, the abdominal musculature, and the thoracic musculature. By the 7th day, there was no trace of intercostal muscle activity. Because of mild subjective respiratory distress and because of the use of the accessory muscles of respiration, artificial respiration had to be considered. Spirometry (Table 1) showed an adequate resting minute volume (8.7 l. per min.) with an adequate tidal volume. On the 10th hospital day, after

TABLE 1. CASE 4.—MINUTE VOLUMES OF A 28 YEAR OLD MAN WITH VENTILATORY DEFICIENCY DUE TO SPINAL POLIOMYELITIS.

Day of illness	*7*	*11*	*11*
Type of respiration	Quiet breathing	Quiet breathing	Maxima effort
Rate per min.	26	30	30
Tidal vol. in cc	335	256	506
Minute vol. l min	8.7	7.7	15.2

progression of the illness had stopped, the minute volume with quiet breathing was still 7.7 l. per min. and on maximal effort was 15.2 l. per min. From the standpoint of respiratory adequacy subsequent recovery was uneventful.

Comment on Case 4. This patient demonstrates the mild peripheral ventilatory deficiency that may occur in acute poliomyelitis. The minute volume on the 7th day exceeded the estimated normal of 6.5 l. per min. for this 63 Kg. man, and indicated that respirator placement was unnecessary. Spirometry subsequently showed that the patient's reserve ventilatory function was almost 200% of his resting value (Table 1). While this showed that he had a great decrease in ventilatory reserve from the normal of 2000% expected in an adult male[19], nevertheless it furnished further evidence that artificial respiration was not needed.

CASE 5. M. S., a 37 year old physician entered the poliomyelitis unit on the third day of an illness beginning with headache, backache, fever, malaise, nausea, and vomiting. Cerebrospinal fluid examination corroborated the diagnosis of acute poliomyelitis. During the succeeding 5 days, paralysis developed in the legs, back, abdominal, intercostal, and diaphragmatic musculature, necessitating placement in a respirator on the 7th day of illness. The acute febrile stage ended on the 9th day. During early convalescence, the respirator was set at 14 cm. of water negative pressure with a rate of 18 per min. This adjustment seemed satisfactory and the patient appeared to be comfortable, although he was unable to remain out of the respirator for periods longer than two minutes. Spirometry was first used on the 33rd day of illness, at which time an adequate ventilation (7.3 l. per min.) was obtained with a negative pressure of 10 cm. of water (Fig. 5). Spontaneous ventilation at this time was only 3.0 l. per min. Subsequently, the negative pressures were gradually reduced, the ventilation being followed by frequent spirometric determinations. By the 60th day after the onset of illness there had been sufficient improvement for the patient to remain out of the respirator for 6 to 8 hours a day. The remainder of the time only 4 cm. of water negative pressure was required to maintain an adequate minute volume (7.6 l. per min.) During the following 2 months the patient was able to tolerate increasingly longer periods out of the respirator, and by 4 months after the onset of poliomyelitis the respirator was no longer required.

Comment on Case 5. Severe peripheral ventilatory deficiency was demonstrated in this patient. The spirometer was of value in determining the proper respirator negative pressures to effect the estimated normal minute volume (7.0 l. per min.) for this 70 Kg. man. The negative pressures used were strikingly lower than in the previous acute cases. If the negative pressures usually recommended for respirator patients (16 to 18 cm. of water at a rate of 18 to 24 respirations per min.[11]) had been used in this patient, hyperventilation undoubtedly would have resulted. An example of this phenomenon can be seen in Fig. 5 when on the 60th day, an increase of negative pressure from 4 cm. to 10 cm. of water

produced a minute volume of ventilation 50% in excess of normal.

In contrast to the previous cases, the chest respirator was quite effective in this convalescent patient. Spirometric studies showed that the same ventilation was effected by a negative pressure 2 to 2½ cm. of water greater than that used in the cabinet respirator (48th day in Fig. 5).

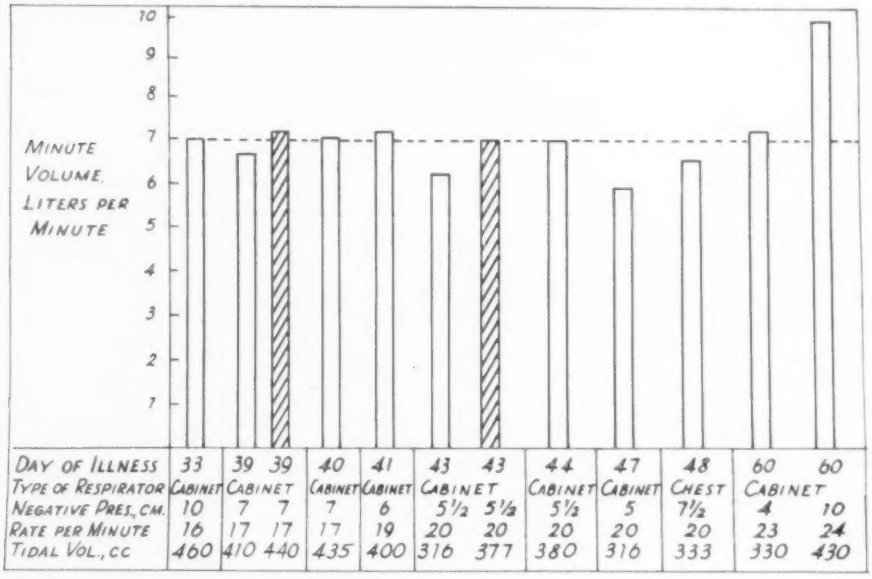

MINUTE VOLUME, LITERS PER MINUTE
10
9
8
7
6
5
4
3
2
1
DAY OF ILLNESS 33 39 39 40 41 43 43 44 47 48 60 60
TYPE OF RESPIRATOR CABINET CABINET CABINET CABINET CABINET CABINET CABINET CHEST CABINET
NEGATIVE PRES., CM. 10 7 7 7 6 5½ 5½ 5½ 5 7½ 4 10
RATE PER MINUTE 16 17 17 17 19 20 20 20 20 20 23 24
TIDAL VOL., CC 460 410 440 435 400 316 377 380 316 333 330 430

FIG. 5. CASE 5.—Bar graph of minute volumes of a 37 year old man with ventilatory deficiency due to spinal poliomyelitis. The dotted line at minute volume of 7.0 l. represents the estimated normal for this patient. The cross-hatched bars indicate the patient's maximal respiratory effort supplementing the support offered by the respirator.

Spirometry was of distinct value in determining this patient's reserve function at particular respirator negative pressures. This was carried out in the same manner as for patients not in a respirator. On the 39th day (Fig. 5) the reserve function was only 107% of the resting value with a negative pressure of 7 cm. of water. Again, on the 43rd day with a negative pressure of 5½ cm. of water, the reserve function was only 118% of the resting minute volume. These determinations showed that the patient's ability to tolerate lower negative pressures was very slight. Any reduction in negative pressures had to be carried out cautiously and with frequent spirometric determinations in order not to exceed the functional capacity of the recovering musculature.

Discussion. Techniques used in the management of respirators have included the application of clinical judgment, arbitrary standards for setting the respirator pressure and rate, chemical studies of the blood, and oximetry. The value of clinical judgment in the treatment of any disease is obvious. However, its limitations in special situations must be clearly recognized. Accurate appraisal of ventilatory function based upon clinical observation and subjective symptoms is possible only in extreme situations. It is clear that arbitrary standards do not take into

account all of the many variables in a particular clinical situation. The inevitable result is to expose the patient to the dangers of subclinical hypoxia or to the difficulties associated with hyperventilation.

There are 2 methods of studying respiratory function by chemical means. The first of these, determination of arterial oxygen saturation, is the more direct method. It has limited value because of numerous technical difficulties. The less direct method, which depends on the determination of serum carbon dioxide combining power, chloride, and pH, yields valuable information but is less sensitive and is time-consuming. Because it is impractical to repeat these determinations frequently, both methods are limited in their application to the study of ventilatory function.

Oximetry as used by Elam *et al.*[7] at present is the best method of determining respiratory adequacy. It is equally useful whether the basic difficulty be ventilatory or alveolar deficiency. Hence, it has a distinct advantage over spirometry which measures only ventilation. The inability to indicate difficulties in gaseous transport across the alveolar membrane constitutes a basic limitation to spirometry. On the other hand, oximetry is limited, not only by scarcity of supply and high initial cost but also by the technical details of standardization and operation.

A relatively new method which is becoming increasingly useful in the study of ventilation is pneumotachography as described by Silverman *et al.*[20]. Unpublished data[8] obtained with this method indicate that errors relating to resistance to gas flow in the spirometer are greater than previously suspected.

In the further consideration of spirometry *per se*, it should be mentioned that reliable standards for resting minute volume upon which the calculation of ventilatory adequacy depends, are not available in the published literature. Physiological textbooks commonly give values of 6 to 8 l. per min., but the data in support of these figures are meagre[12]. Ornstein *et al.*[19] give 7.5 l. per min. as the resting minute volume in adults. Leiner[16] presents data on adult tuberculous patients that show resting minute volumes ranging from 4.0 to 8.8 l.per min. No standards for children have been found. No workers have related minute volume to body weight or other body mensuration.

Since it is obvious that ventilation must vary with body size, the normal values for resting minute volume were, for the purposes of this study, estimated on the basis of weight by the previously mentioned formula of Swann[24]. To do this, the following assumptions were made: first, the resting minute volume for a 70 Kg. man is 7.0 l. per min.; second, the resting minute volume is directly related to the surface area of the body; and finally, the data of Kleiber[14] is applicable, namely that the body surface may be related to the three fourths power of the body weight. The possible inaccuracies inherent in these assumptions are realized; nevertheless, in the absence of other standards the use of this formula seemed justified.

Another factor limiting the accuracy of spirometric methods is physiologic dead space of respiration. A given tidal volume provides effective alveolar ventilation only in so far as it exceeds the physiologic dead space. Since this uses up approximately 33% of the tidal volume of quiet breathing, as shown by Fowler[9], it is apparent that a small tidal volume with a rapid rate will produce less effective alveolar ventilation than a larger tidal volume with a slower rate, even though the minute volume remains the same.

The changes, demonstrated by Fowler, in the size of the physiologic dead space would have little practical importance in the type of problem under discussion. A small tidal volume and rapid rate are ordinarily met only in a patient who is not in a respirator. It must be kept in mind, however, that under such circumstances an adequate minute volume does not necessarily indicate adequate alveolar ventilation.

Summary and Conclusions. 1. Spirometry offers a simple method for determining respiratory adequacy in various types of ventilatory deficiency, and is applicable whether or not the patient is in a mechanical respirator.

2. Study of 5 patients with ventilatory deficiency demonstrates the usefulness of spirometry in the following ways: a) in determining the proper respirator settings for effecting adequate ventilation, b) in revealing day to day variations in ventilatory function, c) in giving an objective indication or contraindication for respirator placement, d) in measuring ventilatory reserve, e) in furnishing an objective criterion for removal from the respirator.

3. The value of the respirator in central ventilatory failure is demonstrated.

4. The advantages and disadvantages of various types of management of respirator patients are discussed.

5. Among the limitations of spirometry are included mechanical errors inherent in the apparatus, inability to reveal alveolar deficiency, physiologic dead space, and lack of adequate standards for minute volume of respiration.

6. A method of calculating resting minute volume standards is presented.

Grateful acknowledgment is made to Dr. James O. Elam for his helpful suggestions and technical assistance.

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SINGLE CELL AUTOGRAPHS OF BONE MARROW AND BLOOD FROM RATS USING RADIOACTIVE PHOSPHORUS*

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THE field of autoradiography offers biology and medicine a new tool for investigation which at present is a source of increasing interest. Autoradiographs of single cells as applied to hematological material are a very recent accomplishment. The present study was undertaken to explore the feasibility of single cell autographs of bone marrow cells in rats using P^{32}. The principle underlying the investigation depends upon the fact that radioactive phosphorus is deposited in the bone marrow. If the marrow is smeared upon a photographic emulsion the marrow cells containing the phosphorus may be recognized microscopically after suitable exposure, development and staining.

Methods. Albino rats of the Wistar strain, 2 to 5 weeks of age, weighing 12.5 to 54 gm. were used. The diet consisted of oats and fox chow.

Serial bone marrow samples from the femora, using the method of Cameron and Watson[3], were obtained on each animal. A sample of peripheral blood from the tail was taken concomitantly. Up to 4 samples were obtained in the first 24 hours and at appropriate intervals thereafter until death or sacrifice of the animal. The puncture sites on the femur were at least 4 mm. apart.

Carrier free radioactive phosphorus† (P^{32}) was obtained as phosphoric acid and diluted with Ringer's solution for subcutaneous injection. Table 1 records the weight, sex, dose used and survival time of each animal. The rats are numbered in the same order in which the experiments were performed. If bacteria were seen in an antemortem smear of blood the word "bacteremia" was added. Eleven preparations from 3 control animals were obtained and treated in a manner identical with the test preparations. One of these 3 animals received a total of 2000 r of roentgen irradiation (kv 200, ma 20, distance 50 cm., portal 7x7 cm., hvl 0.9 cu., filter 1 cu x 1 al, rpm 45), 1000 r at the beginning of the observation period and 1000 r 24 hours later.

TABLE 1.—WEIGHT, SEX, DOSAGE AND SURVIVAL PERIOD OF ANIMALS

Rat	*Weight (in gm.)*	*Sex*	*Dose (in uc.)*	*Dose corrected for body wt. (uc. per gm.)*	*Survival Time (in hrs. or days)*
12	54	F	500	9.3	4 days (bacteremia)
11	38	F	500	13.2	8.5 hrs. (sacrificed)
8	37	F	500	13.5	10 days
9	33	F	500	15.2	7 days (bacteremia)
14	12.5	M	300	24.0	19 hrs.

Eastman Type NTB nuclear track plates were used, following the method of Boyd *et al*[2]. Small samples of blood and of marrow were diluted with Ringer's solution in a syringe to prevent evaporation, the diluted samples having a volume of 0.1 to 0.2 cc. In 2 instances a portion of thymus was broken up in a drop of Ringer's solution and the cell suspension obtained treated similarly to the blood and marrow samples. Within 30 min

* Aided by grant from Ayerst, MacKenna and Harrison.

† From the Atomic Energy Project, National Research Council, Chalk River, Ontario.

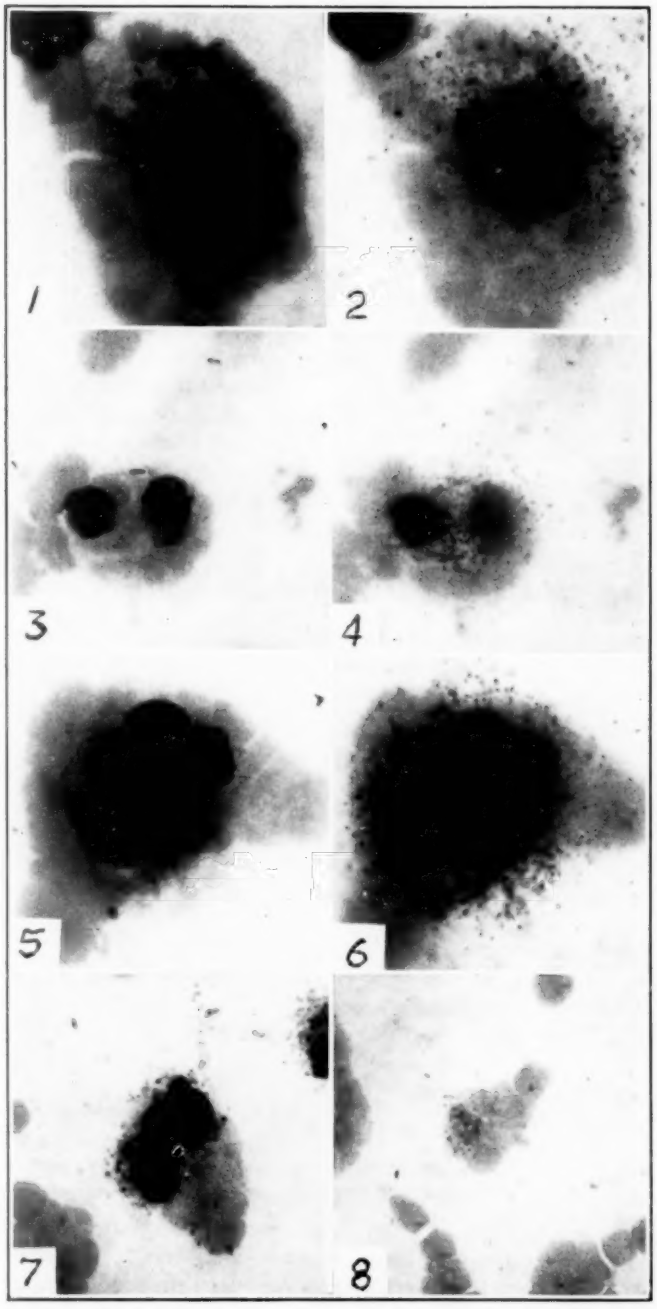

FIG. 1.—Basophilic erythroblast from the marrow 21 hours after exposure to 0.5 mc of P^{32}—focused on the cell. Rat 12. Pappenheim, x 1070.

FIG. 2.—Same as Fig. 1.—focused on the autograph.

FIG. 3.—Two polychromatophilic erythroblasts from the same preparation as Fig. 1.—focused on the cells. Pappenheim, x 1070.

FIG. 4.—Same as Fig. 3.—focused on the autograph.

FIG. 5.—Myelocyte and 2 adjacent bare nuclei from the same preparation as Fig. 1.—focused on the cell. Pappenheim, x 1070.

FIG. 6.—Same as Fig. 5.—focused on the autograph.

FIG. 7.—Polymorphonuclear neutrophils from the same preparation as Fig. 1. also showing autograph. Pappenheim, x 1070.

FIG. 8.—Polychromatophilic erythrocyte from the same preparation as Fig. 1. also showing autograph. Pappenheim, x 1070.

utes the samples were smeared on the emulsion covered surface of the glass plates in a darkroom with the aid of a safelight. Smearing of the samples was accomplished by the use of an ordinary glass slide held at a very acute angle with no pressure applied except that of its own weight. Late in the study it was realized that isolated drops of cell suspension over one portion of the emulsion surface were undesirable, so these were removed with a syringe and needle before being allowed to dry.

Exposure of the slides in a light-tight box varied from 24 to 61 days. The best autographs were exposed for 42 days, but this point was not studied in detail. The next step was fixation in methyl alcohol for 5 minutes, followed by development in Eastman D-19 at 20°c for 1 to 25 minutes, 5 minutes being the usual period. Clearing in 10% sodium thiosulphate required about 40 minutes. After washing, the slides were put in double distilled water for 10 minutes. When well dried (requiring about 1½ hours) the smears were stained by Pappenheim's method. They were not mounted in balsam until thoroughly dry.

Results. Autographs of single blood and marrow cells were obtained after exposure to radioactive phosphorus. In studying the accompanying illustrations (Figs. 1 to 8) of marrow cells smeared on plates covered by photographic emulsion it should be noted that the cellular detail and the autographs are on different planes, as the cells are smeared on top of the emulsion. Therefore separate focusing is frequently required to demonstrate both, as in Figs. 1 and 2 of the same marrow cell.

Some preparations from rat 8 were unsatisfactory, although autographs from cell clumps were obtained. Single cell autographs were obtained from the marrow of rats 9, 11, 12 and 14. These data are presented in Table 2 in order to show the time relationships to the injection of P^{32}.

Autographs arising from clumps containing nucleated cells are not included in the table if single cell autographs were also obtained. In many instances a careful search of the whole slide was made before finding the cell specified in the table. The series of marrow preparations from rat 12 forms a notable exception in that a large number of cells autographed (Figs. 1 to 8).

TABLE 2. AUTOGRAPHS OBTAINED SHOWING TIME RELATIONSHIPS

Rat	*Sample*	*4–6 hrs.*	*8–9 hrs.*	*15–21 hrs.*	*26–29 hrs.*	*39–48 hrs.*	*64–72 hrs.*	*4–5 day*	*7–10 day*
8	Blood						Clumps*		Nil*
9	Marrow				Myelocyte		Clumps†		Nil†
	Blood				Unidentified cell		Degenerate cell		
11	Marrow		Myelocyte						
	Blood	Clumps	Nil†						
12	Marrow	Myelocyte Metamyel. ‡E. Erythroblast ‡L. Erythroblast	Myelo. Metamyel. Poly. E. Erythroblast	Myelo. Metamyel. Poly. E. Erythrobl. L. Erythrobl. R.B.C. polychrom orthochrom Megakaryocyte		Myelo. Metamyel. L. Erythroblast		L. Erythroblast	
	Blood	Clumps		R.B.C. polychrom		L. Erythroblast		Myelo. L. Erythroblast R.B.C. polychrom	
14	Marrow		Myelo. Metamyel.	Myelocyte Metamyel. L. Erythroblast					
	Blood Thymus	Clumps	Nil†	Myelocyte Lymphocytes Reticulum cells					

* Stain poor.
† Sample poor in nucleated cells.
‡ Early erythroblast is basophilic. Late erythroblast is polychromatophilic or orthochromic.

TABLE 3. PERCENTAGE OF EACH MARROW CELL TYPE GIVING AUTOGRAPH

Rat 12

	Pre-injection	*4½ hours*	*8 hours*	*21 hours*	*2 days*	*4 days*
Promyelo.	0	100	100	100	84	
Myelo.	0	75	25	100	25	
Metamyel.	0	70	14	84	33	
Poly. Neutro.	0	0	16	78	0	
*E. Erythrobl.	0	80	28	92	0	0
*L. Erythrobl.	0	30	0	42	7	28
Lymph.	0	0	0	14	0	
Eos.			0			
Unidentified		0	0	33	0	0
Polychromat. erythrocytes	0	0	0	46	0	0

* Early erythroblast is a basophilic erythroblast
Late erythroblast is polychromatophilic or orthochromic

Table 3 records the percentage of each cell type that autographed from the most suitable part of each smear from rat 12. Two lines under a figure indicates that the majority of that cell type autographed intensely; one line indicates a moderately intense autograph for the majority of cells; and figures without a line indicate a faint autograph for the majority. A very few cells were so obscured by the silver granules that they could not be identified.

Before interpreting these results certain other observations should be noted.

Emulsion Factors. The preparations varied considerably both in the production of autographs and in their intensity. This variation occurred not only from slide to slide, but also to a lesser degree on the same slide when comparing areas only a millimeter apart. The correction of this defect is very desirable. It was found that a uniform distribution of the cell suspension at the time of smearing with avoidance of pooling is one of the requirements.

Background fog can be focused out if the autograph is most intense at the emulsion surface. For unknown reasons sometimes the autograph is only identified below the surface where background fog is more likely to obscure it. Of the numerous types of scratches and artefacts formed by the aggregates of silver granules, only occasionally does one resemble an autograph. On one control slide such an artefact was underlying a cell so that the only feature permitting its true identification was a refractile particle overlying the cell. Not infrequently artefacts were apparently caused by minute refractile particles which were directly over them.

Controls. The following control samples were smeared on Type NTB plates:

Three marrow samples from 2 rats (60 gm. and 37 gm.).

Three marrow samples and 3 peripheral blood samples from a 13.5 gm. rat following roentgen irradiation, using the intervals of 5 hours, 29 hours and 5 days after irradiation.

One marrow sample and 1 blood sample from the 13.5 gm. rat taken 4½ hours after being sacrificed.

Nothing indistinguishable from an autograph was seen in any of the above listed preparations.

STAIN. The autograph preparations usually showed impertections in the stain. In most areas the stain was more basophilic than is optimal. The specific granules of the granulopoietic series almost always failed to stain—more so with the neutrophils than the eosinophils. Certainly more cells remained unidentified with these preparations than with routine blood smears, but most of the cells could be identified after obtaining some experience with the method. Blasts were never recognised with certainty. Some eosinophils were probably recorded as neutrophils.

Returning to Tables 2 and 3, the seemingly significant points may be noted. The quantitative results at different time intervals in Table 3 cannot be compared because the portion of each slide used probably has a different sensitivity. The most intense autographs were obtained with the 21 hour preparation. There it is noted that all of the myelocytes autographed, 84% of the metamyelocytes and 78% of the polymorphonuclear forms. Autographs of the latter were usually less intense. Ninety-two percent of the basophilic erythroblasts autographed, 42% of the polychromatophilic and orthochromic erythroblasts, and 46% of the polychromatophilic erythro*cytes*. Rarely an orthochromic erythrocyte was seen to autograph. A cell in mitosis from this preparation autographed. A megakaryocyte gave a faint autograph around the nucleus which did not reach the cell margin. Although autographs of 14% of the lymphocytes is recorded, their identity is not as certain as that of the other cells.

The polychromatophilic (and rarely orthochromic) erythrocytes never gave more than relatively faint autographs. They failed to autograph in all the marrow preparations of rat 12 except one. In this 21 hour slide they autographed in only a few areas. One of these cells autographed in the concomitant blood sample. The fact that they showed up again in the peripheral blood preparation of this animal at 4 days seems to illustrate further the lack of uniformity in the autograph sensitivity.

Other interesting observations from Table 3 are that both granulocyte and erythrocyte precursors autographed at 4 hours. It may be significant that the polymorphonuclear neutrophils did not autograph at this time. Failure of basophilic erythroblasts to autograph in the 2 and 4 day samples may result from the diminishing plasma concentration of P^{32}. The later erythroblasts perhaps autograph because their percursors contained a high concentration of P^{32} (24 or more hours previously). An autographing polychromatophilic erythroblast was found in the peripheral blood of this animal at 2 days and again at 4 days.

In striking contrast to all the other animals, where at best a small number of single cell autographs could be found, the marrow samples from rat 12 autographed very well. Rat 12 received a smaller dose of P^{32} per gm. of body weight than any other animal used for NTB plate preparations. Its diet or surroundings were not obviously different from the other animals.

An additional feature to be noted in Table 2 is that in the peripheral blood some clumps of cells, always including some leukocytes, autographed at 4 hours. A myelocyte in the peripheral blood of rat 12 autographed 4 days after exposure, and a few other instances of peripheral blood single cell autographs are noted in Table 2.

The cell suspension from the thymus of rat 14 at 19 hours resulted in a few faint but definite autographs. None of the cells were well preserved, and they were thought to be degenerating. No cytoplasm could be seen around the lymphocyte nuclei. A very few of these nuclei autographed. Other larger

lighter nuclei with more irregular outline may have been from the reticulum cells. Several of these autographed faintly.

Discussion. This is the first report to our knowledge of single cell autographs being obtained from rat marrow elements and peripheral blood cells using P^{32}. Single cell autographs of peripheral blood cells using C^{14} labeled glycine have been reported[2]. Stevens, working in Leblond's laboratory, has recently obtained autographs of marrow cell suspensions using P^{32} in rats[5].

Technical features have been the central issue in the present investigation with no effort to focus on any specific hematological problems. However, some conclusions may be tentatively stated.

The much greater uptake of P^{32} by the marrow cells of rat 12, as indicated by the autographs, is of interest. The need of the cell for phosphorus and the availability of P^{31} are important considerations in this regard. It is reported that the change of diet with weaning is associated with a very temporary increase in phosphorus excretion in rats[1]. It is possible that such a mechanism, reflecting more available phosphorus, prevented a more favourable uptake of P^{32} in the recently weaned rats 8, 9, and 11 (33 to 38 gm.) as compared with rat 12 (54 gm.). This does not explain the fact that rat 14 (12.5 gm.) failed to give very high concentrations as indicated by the autographs in spite of the larger dose administered.

Concerning intracellular localization, only the following may be said: For one megakaryocyte the autograph apparently localized over the nucleus, but other megakaryocytes did not show this feature. Evidence for a significant cytoplasmic concentration in erythropoietic cells seems to follow from the occurrence of autographs of polychromatophilic erythrocytes.

The concept of a threshold concentration of P^{32} below which single cell autographs are not obtained with the method used must be borne in mind. It is very possible that erythrocytes can take up some P^{32} after reaching the peripheral blood as suggested by the very rapid uptake observed for these elements by Erf and Lawrence[4]. Large cell clumps in the peripheral blood did autograph at 4 hours (Table 2), but almost invariably orthochromic erythrocytes failed to autograph individually in the most sensitive preparations.

Among the formed elements of the marrow it may be said that for the small amount of material observed, the basophilic erythroblasts and the myelocytes (and promyelocytes) have a more rapid P^{32} turnover than the megakaryocytes, later erythroblasts and metamyelocytes. Autographs of polymorphonuclear neutrophils and polychromatophilic erythrocytes may be due to maturation after exposure of their precursors to P^{32} or may reflect the rate of phosphorus turnover in these more mature cell types.

The evidence from this study supports the concept that the lymphocytes take up less P^{32} than the young erythroid and myeloid cells. Faint autographs of lymphocytes were seen in preparations of bone marrow and thymic cell suspensions, but none from the peripheral blood. Using data from the total leukocyte and differential counts made when obtaining each specimen, it may noted that rat 12 had 1595 lymphocytes per c.mm. just before the injection of isotope, and 1200 lymphocytes per c.mm. 48 hours later. One would presume that lymphocytes were being released into the blood stream.

Autographs of polymorphonuclear neutrophils from the peripheral blood

were not obtained. Using rat 12, the most suitable animal, this point was not well investigated. The neutrophil count dropped from 2175 per c.mm. before injection to 60 per c.mm. 48 hours later. The post mortem smear at 4 days showed obvious evidence of release of mature granulocytes and their precursors in the blood. The NTB preparation of this 4 day peripheral blood sample contained a rather small number of nucleated cells. No polymorphonuclear neutrophils were identified. About 8 myelocytes were seen of which some were atypical. Contrary to expectation only one of these myelocytes autographed. The explanation of this, of course, may lie in a relatively less sensitive NTB preparation.

A study of histological sections from the group of animals used in this investigation gives the impression that the destruction occurring in the bone marrow is more rapid and more complete than in the lymphatic tissue[7]. In accounting for this difference one must consider the radiation emitted by the P^{32} in bone as well as that from P^{32} within the marrow cells.

A few words may be added about improvements and future applications of the method of investigation under study. Making some rough calculations of theoretical possibility, it is pointed out that the autographs obtained in this study are close to the borderline of possible definition[9]. More sensitive photographic emulsions are highly desirable. The Experimental Type NTB-3 emulsion developed by the Eastman Kodak Company may be a step in this direction. A method detecting tracer doses is needed to obtain results of greater physiological value rather than one detecting lethal doses. It would be of interest, however, if the necessary dose could be brought into the range of therapeutic levels for treating blood dyscrasias so that human material could be studied.

It is also desirable to develop an exact method for uniform optimal development of the photographic emulsion so that results may be compared on a somewhat quantitative basis. With more comparable results from plate to plate further study could be made of the factors affecting P^{32} uptake by individual hemopoietic cells. Knowledge of these variables should make treatment of polycythemia vera and other blood dyscrasias more exact. At times when the cells need more phosphorus, as might occur with a low phosphorus diet, the P^{32} uptake will be greater as will the hemopoietic damage. Perhaps for this reason rat 12 died in 4 days, whereas 2 other animals receiving larger doses survived 7 and 10 days.

Some information might be obtained using the method reported in the study of experimental leukemia in mice. It is reasonable to correlate the lower P^{32} uptake in lymphocytes and their precursors as compared with myelocytes with the fact that lymphatic leukemia responds less well to P^{32} than myelogenous leukemia. However, it is also well known that Roentgen rays and many other agents used in leukemia are more effective in the myelogenous form.

If the method used in this investigation could be applied to the study of desoxyribosenucleic acid turnover in the hemopoietic elements, useful information might be obtained. Leblond, Stevens and Bogorosh[6] have followed desoxyribosenucleic acid turnover in various organs using P^{32} and the autographic method. They treated their tissues to remove water soluble phosphates, phospholipids and, by the use of ribonuclease, also the ribosenucleic acid. Desoxyribosenucleic acid was considered to be the source of most of the remaining phosphorus. There

is evidence that desoxyribosenucleic acid (a fundamental unit in nuclear protein) takes up new phosphorus molecules only during mitosis of the cell. Assuming that with this method autographing cells have been through a mitosis following the injection of P^{32}, one could study mitotic activity in marrow and lymphatic cell suspensions. Except in those conditions where leukocytes might undergo mitosis in the peripheral blood, data might be obtained concerning the life cycle in the peripheral blood of the granulocyte and the lymphocyte. Such data would not yield exact figures, but it would be useful for comparative purposes if the dose of P^{32} required could be lowered substantially.

For some types of animal experimental work, C^{14} labeled glycine seems definitely preferable to P^{32} because of the very small doses required. Boyd *et al.*[2] used 3 uc. in a rat for their autographs of the peripheral blood cells. This tremendous advantage of C^{14} for single cell autographs is largely due to the much lower energy of its beta rays. Many of the C^{14} beta particles will contribute to a single cell autograph, whereas very few of the particles from P^{32} have a low enough initial energy to contribute to this type of autograph[5].

Summary. Single cell autographs of marrow and peripheral blood elements are reported for the first time following the injection of P^{32} in rats.

In the small number of satisfactory preparations studied, the youngest erythropoietic and granulopoietic forms from the marrow have the most intense autographs, indicating rapid phosphorus turnover. Autographs of megakaryocytes and lymphocytes are faint at best.

If the observation of more selective uptake by marrow elements than occurs in the lymphatic system is substantiated, it would suggest that radioactive phosphorus has some advantages over Roentgen ray therapy in myelogenous leukemia.

The technique at present has many limitations. Desirable improvements and some applications to hematological problems are discussed.

The author is indebted to Dr. E. S. Mills for supplying the facilities for this investigation and for advice and criticism. Gratitude is also expressed to Dr. C. P. Leblond and Dr. G. A. Boyd for instruction in their respective techniques.

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FAMILIAL HEMOCHROMATOSIS: WITH COMMENTS ON ADRENAL FUNCTION IN HEMOCHROMATOSIS

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Although the etiology of hemochromatosis is unknown, Sheldon[17] in his classic monograph on the subject concluded that the clinical and pathologic characteristics of the disease were best explained by considering hemochromatosis "an inborn error of metabolism" congenital in origin. Sheldon supported this theory in part by the reports of 14 authors who had recorded a familial or hereditary incidence of the disease. However, Sheldon thought that only 5 of the 14 reports were sufficiently well founded to "provide irrefutable evidence that at times hemochromatosis has a familial incidence."

Since Sheldon's review, Lawrence[12] has reported hemochromatosis in brothers of 3 different families. One of these 3 families was particularly interesting and significant, as the disease developed in identical twins at about the same time. Harvier and coworkers[7] have described 8 cases of hemochromatosis occurring in 4 pairs of brothers. The diagnosis of hemochromatosis in Harvier's cases were made on clinical data alone. John[10] has reported a patient with hemochromatosis whose brother was pigmented, and other authors[11,13,14] have recorded cases of hemochromatosis in which diabetes mellitus was present in some other member of the family. However, the paucity of data makes an evaluation of these cases difficult.

The purpose of this communication is to report a family in which 2 brothers had hemochromatosis proved at autopsy, while a sister is living, has diabetes, but not hemochromatosis. As "cortin" and 17 ketosteroid excretions were determined on 1 patient, some comments are made concerning adrenal function in hemochromatosis.

Case Reports. Case 1. A. M. (B.C.H. 1, 274, 167), age 47, was a painter and sandblaster of Irish descent. Five years before admission to the hospital the patient had noted a gradual darkening of his skin, loss of pubic and axillary hair, and the development of impotence. However, he felt well enough to work steadily until 1 month before admission to the hospital, when he received an accidental blow on his head while working. During convalescence from this injury he developed diarrhea, crampy right lower quadrant abdominal pain, and weakness. The bowel movements were slightly watery but did not contain visible blood. The patient also had anorexia and lost weight but did not notice any polydipsia or polyuria.

The patient's past history was non-contributory, including only childhood diseases, occasional colds and minor injuries. His alcoholic intake was slight.

Physicial examination revealed a well developed, poorly nourished chronically ill appearing individual. His skin was dry, of poor elasticity, and deeply pigmented. The pigmentation was brown with a slight blue tinge and generalized, although it was darkest over his forearms and hands. Axillary, pubic and body hair was absent. A few small telangiectases were observed on the upper chest but there was no detectable icterus. The buccal mucosa showed small scattered areas of blue-brown pigmentation. Examination of the heart and chest revealed nothing remarkable. The blood pressure was 138/62, pulse 65. The liver was hard, slightly tender and

extended to the pelvic brim and far into the left upper quadrant. The spleen was felt 2 fingerbreadths below the left costal margin. No other organs or masses were felt in the abdomen. Both testicles were small and soft. Rectal and neurological examinations were negative.

Laboratory Data. The urine was amber, acid in reaction with a specific gravity of 1.012. Tests for albumin and sugar were negative, while urobilinogen was present in the dilution of 1:128. The urinary sediment was negative. The hemoglobin was 10 gm. and the red count 3,670,000 cells per c.mm., with an hematocrit of 32%. The white blood count was 9100 cells per c.mm., with a normal differential. The icterus index was 14 and the non-protein nitrogen 26 mg. per 100 cc. A glucose tolerance test (100 gm. of glucose orally) showed a fasting blood sugar of 113 mg. with a rise of 218 mg. in 1 hour and a return to normal (106 mg.) in 2 hours. The total protein was 6.96 gm.%, the prothrombin time 76% of normal, and the cephalin flocculation 1 plus. A bromsulphalein test (5 mg. per kg.) showed 6% retention in 45 minutes. The basal metabolic rate was + 2%. Urinary "cortin" excretion[2] was 1.2 mg./24 hours, (normal 1 to 2 mg./24 hours) and the excretion of 17 ketosteroids was 1.5 mg./24 hours. The serum iron was 205 γ gm./100 cc. (average normal 100 γ gm./100 cc.)[15] and the total iron carrying capacity was 300 μgm./100 cc. (average normal 300 μgm./100 cc.)[15*].

A punch biopsy of the liver (Fig. 1) showed marked pigment cirrhosis with massive iron deposition.

Although the patient had 3 additional hospital admissions before his death, his subsequent course may be summarized as follows: There was a rapid deterioration of the patient's carbohydrate metabolism as evidenced by the fact that 3 weeks following his first hospitalization his fasting blood sugar was 117 mg. and 6 days later 270 mg. He finally required approximately 50 units of insulin per day for the control of his diabetes. The patient later developed ascites which was treated by a low-salt diet and mercurial diuretics. A second estimation of the "cortin" excretion during the latter part of his illness was 5.2 mg./24 hours.

The patient succumbed to a massive gastrointestinal hemorrhage, 9 months after the diagnosis of hemochromatosis had been made.

At *autopsy* the liver weighed 3500 gm. and its surface was hard and nodular, the nodules being 1 to 2 mm. in diameter. It cut with increased resistance and had a tawny red cut surface. The liver, lymph nodes, kidney, pancreas, heart and spleen (Fig. 2) showed strongly positive iron reactions when treated with potassium ferricyanide and hydrochloric acid.

The gastrointestinal tract was filled with a large amount of blood, the greatest concentrations being found in the stomach and in the terminal ileum. In the esophagus at the level of the diaphragm, there was a small erosion that was the apparent site of bleeding although no gross esophageal varices were demonstrated. The adrenal glands were normal to gross examination as were the testes except for the small size of the latter.

Microscopic examination of the skin showed small deposits of melanin in the basal layers of the stratum malphigian. In addition, some epithelial cells of the sweat glands and macrophages of the corium contained hemosiderin. Sections of the liver, pancreas, heart, lymph nodes, gastrointestinal tract, kidneys, and choroid plexus contained iron pigment that was accompanied by extensive fibrosis in the liver, pancreas, and lymph nodes.

The deposition of iron pigment in the adrenal glands was limited to the zona glomerulosa (Figs. 3 and 4). Moderate amounts of hemosiderin were found in all cell types of the anterior pituitary gland. In the testes, no iron pigment was detected, although it was noted that there were few spermatogenic cells and no maturing sperm. The number of interstitial cells appeared diminished.

CASE 2. † J. M., a 35 year old surveyor was admitted to the hospital because of repeated attacks of pain in the left upper quadrant of his abdomen for 5 days. Five months before admission he had noted a heavy sensation in his right upper quadrant and that his skin appeared darker than usual. He consulted a physician at this time who told him that his liver was enlarged. During the month preceding admission he had felt weak and lacked his usual vitality.

The patient's past history was non-contributory.

On physical examination the patient was well developed and well nourished. His skin was dry with a diffuse brown gray pigmentation of the face, neck and arms. The buccal mucosa was not pigmented and there was no

* These determinations were done through the kindness of Dr. Clement Finch at the Peter Bent Brigham Hospital, Boston.

† I am indebted to Dr. Walter L. Palmer of the University of Chicago Medical School for the data on this patient.

hyperpigmentation of the axillae, nipples, and genitalia. The eyes, ears, nose and throat were not remarkable. Numerous small discrete non-tender cervical and submaxillary lymph nodes were palpable.

The blood pressure was 115/90. Examination of the heart and lungs was negative. The liver was palpated 4 fingerbreadths below the right costal margin and was smooth and non-tender. There were no other palpable masses or organs in the abdomen. Rectal and neurological examinations were negative.

A urinalysis was negative, including a Rous test for hemosiderin. The red blood count was 3,500,000 cells per c. mm. and the hemoglobin 75%. The white blood count was 9900 cells, with a normal differential count. A glucose tolerance test and a bromsulfphalein test were within normal limits.

The patient was discharged with a diagnosis of hemochromatosis and did moderately well for 2½ years. He was then admitted to a community hospital because of a gastrointestinal hemorrhage and died shortly thereafter.

An *autopsy* done by the Department of

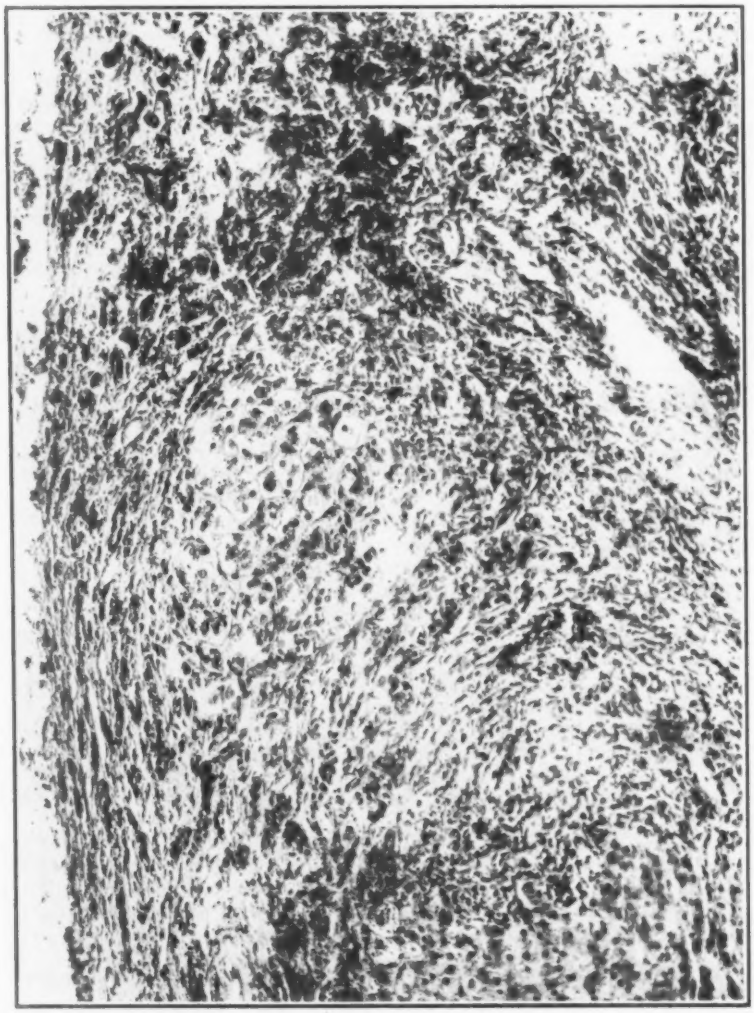

FIG. 1.—Punch biopsy of the liver (Pt. A. M.) showing extensive iron deposition and fibrosis. Hematoxylin and eosin (x 140).

Pathology of the University of Chicago confirmed the diagnosis of hemochromatosis and gastrointestinal hemorrhage. The liver weighed 4923 gm. and was nodular and fibrotic. The gastrointestinal tract contained a large amount of blood. *Microscopic sections* revealed pigment deposition in the patient's liver, pancreas, lymph nodes, myocardium, thyroid, kidney, zona glomerulosa of the adrenals, thymus and salivary glands.

CASE 3. T. M. K., a 52 year old widow, had diabetes which was discovered 3 years ago when the patient was hospitalized for gangrene of a toe on her left foot. Her diabetes was well controlled with 35 units of protamine zinc insulin daily, and following an amputation of her toe she was discharged.

Two years later the patient had a cholecystectomy for right upper quadrant pain. At operation, no note of the state of the liver was reported. Since this operation the patient's insulin requirements have decreased until at the present time she is well controlled on 8 units of protamine-zinc insulin daily and a 2000 calorie diet.

A recent physical examination revealed a well developed, well nourished middle aged woman. Her skin showed no abnormal pigmentation. Examination of her ears, nose, throat, and mouth was negative. Her left eye was the site of a cataract and the fundus of the right eye showed moderate arteriovenous nicking as well as 1 small hemorrhage and 2 small areas of patchy white exudate.

The blood pressure was 180/90. The lungs were normal to percussion and auscultation and examination of the heart showed slight enlargement to the left.

In the right upper quadrant of the abdomen there was a well healed scar. The liver edge was palpated 1 fingerbreadth below the right costal margin and was slightly tender to palpation. No other palpable masses or organs were present in the abdomen. The remainder of the examination was non-contributory.

A urinalysis showed a green reduction with Benedict's solution and a Rous test for hemosiderin was negative. A red blood cell count, hemoglobin and white blood cell count were within normal limits.

In order to determine if this patient had hemochromatosis, a punch biopsy of the liver was done. It showed a normal appearing liver without evidence of pigment cirrhosis or iron deposition.

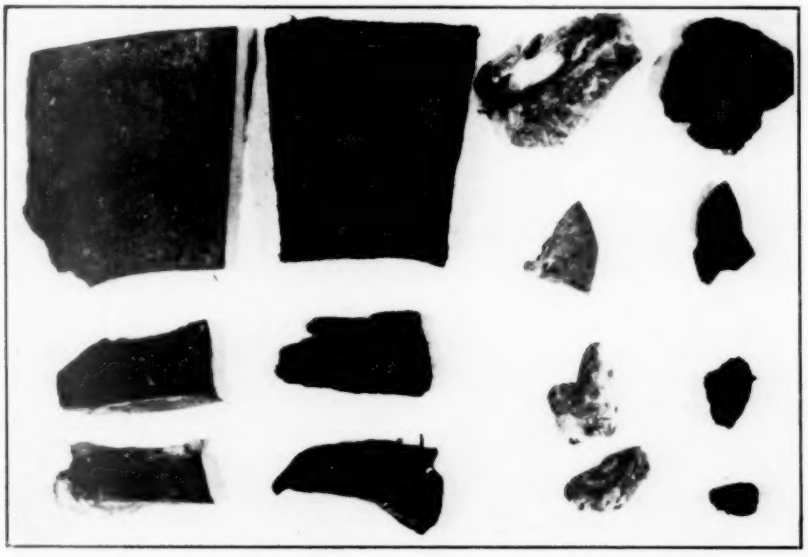

FIG. 2.—Portions of organs (Pt. A. M.), removed at autopsy and treated with potassium ferricyanide and hydrochloric acid, showing positive iron reactions. The left hand column shows untreated, the one next to it, treated portions of liver, spleen and myocardium; the next 2 columns show the same for pancreas, kidney, and lymph nodes.

Other members of this family were investigated as far as possible with the following findings. The father of the above patients died at 86 of a "natural death" and the mother of a "shock" at 76. Of the 2 other siblings of the reported patients, 1 is alive and well, and 1 is dead, the cause of the latter's demise being unknown. Neither of these siblings had any children.

Patient A. M. had 9 children ranging in age from 6 to 19 years. Seven of these children have been examined and none exhibited any detectable

FIG. 3.—Low power view of an adrenal of patient A. M. Note the localization of iron to the zona glomerulosa. Hematoxylin and eosin (x 40).

abnormalities. Another of the children is in active service in the Navy at the present time.

Patient J. M. had 3 children, 1 of whom died in infancy. Patient T. M. K. has 3 living children. Although none of these latter 5 offspring has been examined, each is allegedly well.

Discussion. The incidence of familial hemochromatosis and its implications in the pathogenesis of this disease have been reviewed in the introduction of this paper. Suffice it to say that the present cases add another instance in which hemochromatosis has been found in brothers and in these cases

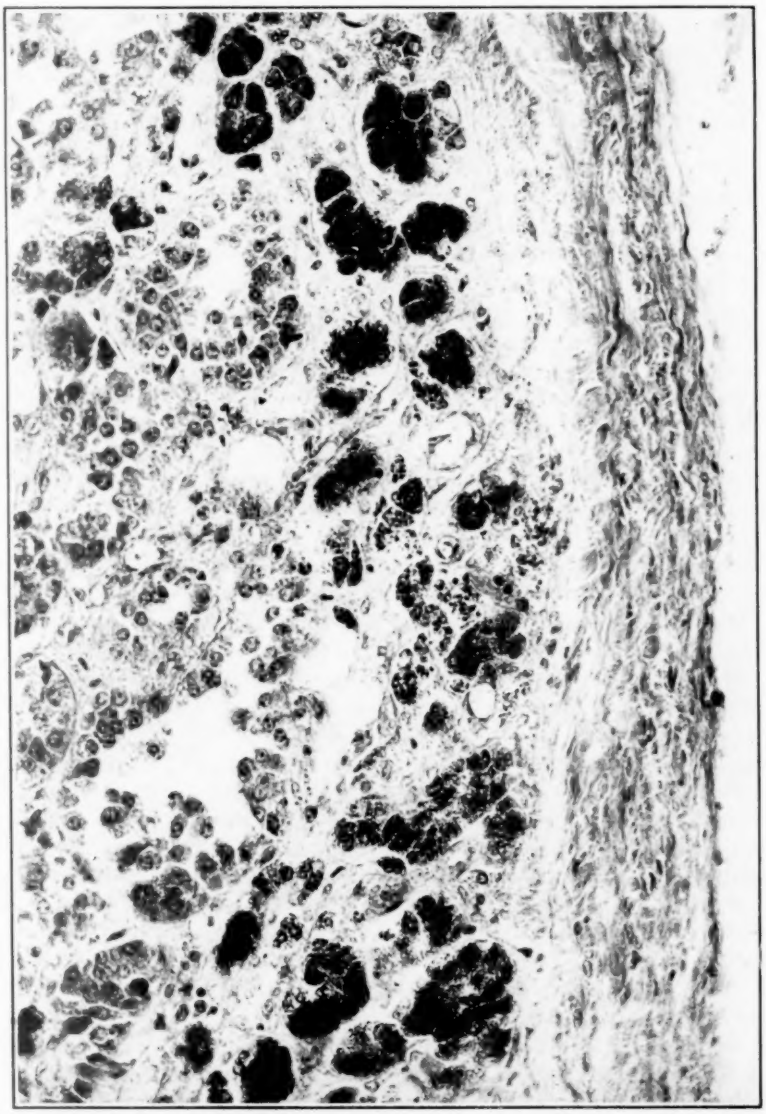

FIG. 4.—High power view of adrenal (Pt. A. M.) showing iron deposition in the cells of the zona glomerulosa. Hematoxylin and eosin (x 300).

confirmed by autopsy. However, the report of this family should also interject a note of caution in the evaluation of familial hemochromatosis. Several authors have assumed that if an individual was found to have hemochromatosis and a member of his family had some stigmata of hemochromatosis (namely diabetes or pigmentation) that the latter also had the disease. Patient T. M. K. is an example of the possible danger that this assumption involves, as she had 2 brothers with proved hemochromatosis, has diabetes, and a palpable liver; yet a liver biopsy, the most reliable clinical test for hemochromatosis, was negative for any evidence of this disease.

It is generally agreed that the pigmentation that occurs in hemochromatosis is due to the deposition of both hemosiderin and melanin in the skin.

The presence of hemosiderin in the skin is not surprising, but the reason for increased melanin pigmentation is less clear. As Addison's disease is accompanied by increased melanin pigmentation, it has frequently been stated that in hemochromatosis the deposition of hemosiderin in the zona glomerulosa of the adrenal is the cause of the abnormal melanin pigmentation. Hellier[8] found in 57 cases of hemochromatosis that 35 had increased melanin pigmentation, and that of these 35, all had iron deposition localized to the zona glomerulosa. However, aside from the melanin pigmentation and a tendency to hypotension, other evidence of adrenal insufficiency is almost always lacking[18], although occasional cases have been reported[9].

Patient A. M., who had both increased melanin pigmentation and characteristic deposition of iron in the zona glomerulosa of his adrenals, excreted 1.2 mg. and 5.2 mg. of "cortin" on 2 respective determinations. As the first determination is within normal limits and the second considerably above normal, although consistent with an individual who was ill, the deposition of hemosiderin in his adrenals did not result in a decreased "cortin" excretion. The method[2] used to determine "cortin" correlates in general with the excretion of the "glycogenic" corticoids, so the lack of other adrenal components could be responsible for the melanin pigmentation. However, the "electrolyte-controlling" hormone, desoxycorticosterone, has little if any effect on the pigmentation of adrenal insufficiency, and, as far as androgenic fractions are concerned, a lack of them (as in hypogonadism) tends to cause decreased pigmentation, an opposite situation from that of hemochromatosis. Because of the above observations some question must be raised concerning the theory that adrenal involvement in hemochromatosis is the cause of the increased melanin pigmentation. Other factors such as the local deposition of iron in the skin with subsequent irritation and changes in oxidation-reduction systems may play the predominant role.

On the other hand, if the deposition of hemosiderin in the zona glomerulosa *is* the cause of the melanin pigmentation in hemochromatosis, it is a remarkable localization of that portion of the adrenal cortex that is responsible for pigment changes in adrenal dysfunction. Evidence that respective zones of the human adrenal cortex produce steroids having different actions is meager. Blackman[1] found hyperplasia of the zona reticularis alone in 9 cases of the adrenogenital syndrome, thus suggesting that this zone is the source of the androgenic hormones. Although Deane and collaborators[3,4,6] have presented evidence from experiments on rats that the salt regulating hormones of the adrenal cortex are elaborated by the zona glomerulosa and the carbohydrate regulating hormones from the

zona fasciculata, the latter zone alone being under pituitary control, there are objections to the applicability of these findings to human adrenal function and morphology. When pituitary adrenocorticotropic hormone is administered to humans, there is evidence that the excretion of electrolyte controlling, carbohydrate regulating and androgenic hormones are all increased[5], and secondly in the histologic examination of the adrenals of individuals with pituitary insufficiency, selective atrophy of the fasciculata with preservation of the glomerulosa is not noted[16].

Summary. The occurrence and significance of familial hemochromatosis is reviewed. Two cases of hemochromatosis occurring in brothers and confirmed at autopsy are presented. A female sibling who had diabetes and an enlarged liver but did not have hemochromatosis is also presented.

In 1 patient with hemochromatosis, melanodermia, and hemosiderin deposition of the adrenal cortex, the amount of "cortin" excreted was found to be within normal limits on 1 occasion and above normal on another. A discussion of these "cortin" values and melanin pigmentation in hemochromatosis leaves the problem of their relationship undecided.

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CLOT RETRACTION. ITS PHYSIOLOGICAL AND CLINICAL SIGNIFICANCE*

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Soon after the discovery that the number of platelets was reduced in certain types of purpura, Hayem[10] made the important observation that clot retraction did not occur following the clotting of thrombocytopenic blood. His finding was confirmed by Bordet and Delange[4], LeSourd and Pagniez[19], Opitz and Schober[22], Fonio[5], and others. It was further established that only intact phatelets were capable of bringing about clot retraction.

In spite of these convincing experimental findings, which clearly suggested that platelets were the key factor in clot retraction, a number of workers, including Achard and Agnaud[1], Roskam[31], Howell[16], Hirose[11], Pickering and Hewitt[23], postulated that retraction was an inherent property of the fibrin gel, with platelets playing either no or only a subsidiary role in this process. While it is certain now that their conclusions were based on experimental results that were technically faulty, their views continue to have adherents. Thus, Mackay[20] in 1931 wrote: "In retraction of the clot the platelet is of secondary importance and serves to augment the retractile property of the fibrin." Lampert[17] expressed a similar view: "In summary one can state that thrombocytes can influence retraction, but the process also occurs without them" (Author's translation).

It is to be remembered that the period during which the platelets were relegated to a minor position or entirely eliminated from consideration in the coagulation reaction, coincides fairly well with the time when the application of colloid chemistry to biology was enthusiastically but often uncritically accepted by physiologists and clinicians. Clot retraction was regarded as analogous or identical with syneresis, a phenomenon of shrinking observed in a colloidal gel. Actually the fibrin clot cannot be classed as a colloidal gel. A number of investigators, particularly Stübel[33] and Howell[15], showed by microscopic studies that the formation of fibrin resembles true crystallization, and furthermore the clot itself is a reticulum of fibrin strands and not an amorphous mass as is a true colloidal gel.

The problem of how platelets cause clot retraction has not been solved. LeSourd and Pagniez[18] in 1906 postulated that platelets furnished a ferment which caused the fibrin to retract. A similar concept was expressed by Glanzmann[8], who named this hypothetical enzyme retractozyme and postulated that platelets having a deficiency of this agent were responsible for a disease which he designated as thrombasthenia. The hypothesis of a specific clot-retracting enzyme is difficult to reconcile with the known fact that only intact platelets are capable of causing clot retraction. Frank[7] in 1911 explained the action of platelets as mechanical. According to his view,

* This work was supported by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U.S. Public Health Service.

little clumps of platelets anchor in the knots of the fibrin net and as they shrink cause contraction of the clot as a whole. A similar concept was later developed by Tocantins[34].

In the investigations reported in this paper the function of platelets in clot retraction was restudied and the probable role of clot retraction in hemostatis and venous thrombosis is considered.

PRINCIPAL FACTORS INFLUENCING CLOT RETRACTION. Recently Quick, Shanberge and Stefanini[30] showed that the speed and degree of clot retraction is proportional to the number of platelets. In their experiment they employed native plasma obtained by collecting and centrifuging blood in silicone-coated glassware. Since no reagents were added, and since only the number of platelets were varied, their findings may be taken as direct proof that clot retraction is proportional to the platelet count, provided other factors are maintained constant. In order fully to evaluate clot retraction, it becomes necessary to determine the secondary factors that influence this process.

The simplest approach to the problem is to determine whether clot retraction can occur in a system consisting of purified fibrinogen, washed platelets and thrombin. The following experiment was carried out.

Procedure. Normal human blood was collected in silicone-coated glassware. One volume of 0.2 M. sodium citrate was mixed with 9 volumes of blood. After centrifuging at 800 r.p.m. for 15 minutes, the plasma rich in platelets was removed and recentrifuged at 4000 r.p.m. The plasma was poured from the packed platelets. The latter were resuspended in 0.85% sodium chloride solution and again packed by centrifugation.

The fibrinogen was salted out from the platelet-poor plasma by mixing it with 1.2 volumes of saturated NaCl solution. After allowing the mixture to remain in an ice bath for 30 minutes, the fibrinogen was packed by centrifugation. It was washed with half saturated NaCl, and after all the solution was removed, it was redissolved and made up to 80% of the original plasma volume. The washed platelets were resuspended in the solution of fibrinogen. Aliquots of 2 cc. of this suspension were put in a series of test tubes to which increasing amounts of thrombin were added. From the results in Fig. 1, it can be seen that when the amount of thrombin added is very small, complete coagulation results, but no clot retraction occurs. When the quantity of thrombin is increased, clot retraction is produced and becomes proportional to the volume of thrombin added.

A reasonable explanation for the effect of thrombin on clot retraction is as follows: Platelets in the absence of thrombin are quite stable even in contact with a foreign surface. Fonio[6] noted that thrombin caused platelets to form pseudopods and increased their adhesiveness with the result that they became fixed to fibrin needles and disintegrated. Quick and Favre-Gilly[29] noted that thrombin was promptly removed from blood by fibrin through adsorption. It can be postulated that if the amount of thrombin is relatively high, the fibrin strands become saturated and some thrombin will appear on the surface. Platelets coming in contact with this surface layer of thrombin, will adhere, undergo metamorphosis and ultimately disintegrate. In this process the fibrin strand to which the platelet is firmly attached becomes twisted, bent and shortened. Whether this is brought about purely by mechanical means or is the result of physicochemical changes remains undetermined. If the amount of thrombin is low, little of it appears on the surface of the fibrin strands, and therefore few platelets adhere and disintegrate. This results in a non-retractile clot.

While the explanation for the effect of thrombin on clot retraction is hypothetical, the results presented in Fig. 1 show unequivocally that the concentration of thrombin quantitatively influences the completeness of clot retraction.

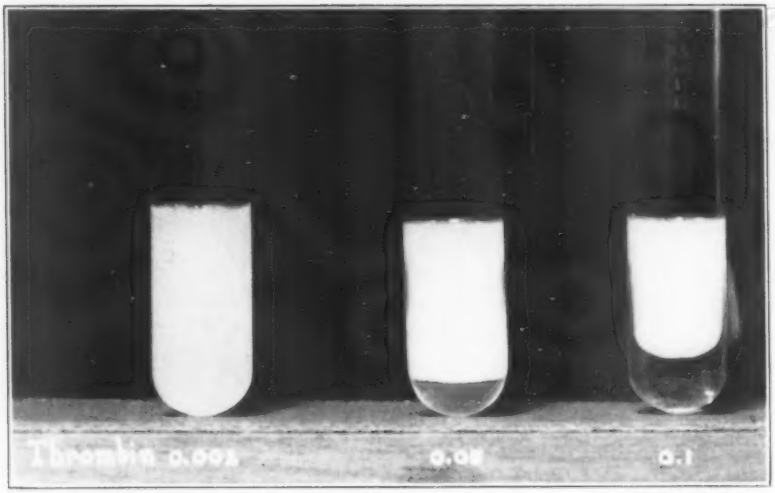


FIG. 1.—The Influence of the Concentration of Thrombin on Clot Retraction.

Thrombin was added to a suspension of washed human platelets in a solution of purified fibrinogen. Retraction can be attributed to the adsorption of thrombin to fibrin which produces a surface on which platelets adhere, coalesce and disintegrate.

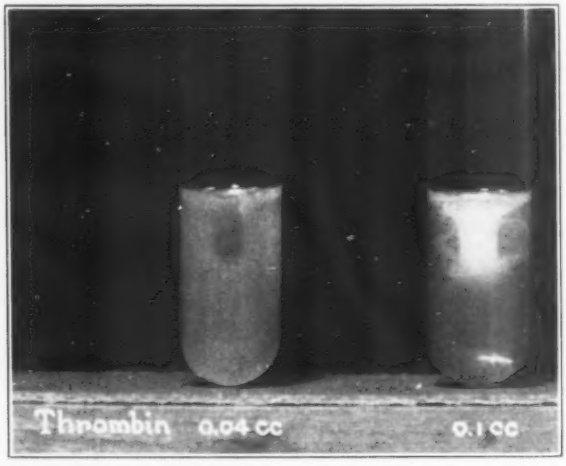


FIG. 2.—The Effect of Adding Thrombin to Native Platelet-Rich Hemophilic Plasma.

A small amount of thrombin was added to Tube 1. It caused the formation of a clot which rapidly contracted to a very small nub that can be faintly seen on the surface. The initial clot removed all the platelets, therefore the secondary clot failed to contract. In Tube 2 enough thrombin was added to coagulate nearly all of the fibrinogen immediately. A veil of fibrin formed about the primary clot, because on retraction it expressed a serum containing thrombin.

When thrombin is added to native hemophilic plasma rich in platelets, clot retraction occurs promptly and the clot shrinks to a small nub, which later becomes surrounded by a secondary clot (Fig. 2). This experiment again illustrates that thrombin is essential for clot retraction. The secondary clot is the result of thrombin in the serum expressed from the clot.

Clot retraction is usually measured in glass test tubes. In 1940, Hirschboeck[12] observed that when blood is put into a vessel coated with collodion, coagulation was delayed and clot retraction failed to occur. Other surfaces such as paraffin and silicone which also cause a delay in coagulation, do not inhibit clot retraction. The peculiar effect of collodion has remained a puzzle. It is obvious that the fibrin becomes so firmly attached to the collodion surface that it resists the internal retractile force of the clot. Recently Quick[28] has found that collodion, like fibrin, absorbs thrombin; he has explained the anti-coagulant action of this surface by its property of removing thrombin, thereby preventing the thrombinogenic chain reaction. As the collodion surface accumulates thrombin, platelets will begin to adhere; when they disintegrate and initiate clotting, the fibrin will be firmly attached with the platelet debris acting as a cementing medium. In Fig. 3, the influence of glass, silicone, lusteroid, and collodion surfaces on clot retraction is shown. In the fifth tube, which was coated with collodion, thrombin was added to augment the retractile force, with the result that some retraction did occur.

It is generally known that clot retraction is influenced by the hematocrit reading. The reason is obvious. The cells constitute a non-retractile mass, and the greater the cell volume of the blood the more the force required to compress the cell and fibrin coagulum. If the force remains constant, but the cell volume is varied, the retraction becomes proportional to the hematocrit reading, as shown in Fig. 4. This explains why anemic blood exhibits greater clot retraction than does normal blood, a fact which has clinical significance as will be discussed later.

The results of the present study, as well as earlier findings, clearly show that clot retraction is dependent upon 4 factors: 1, the number of platelets; 2, the concentration of thrombin; 3, the surface surrounding the clot; and

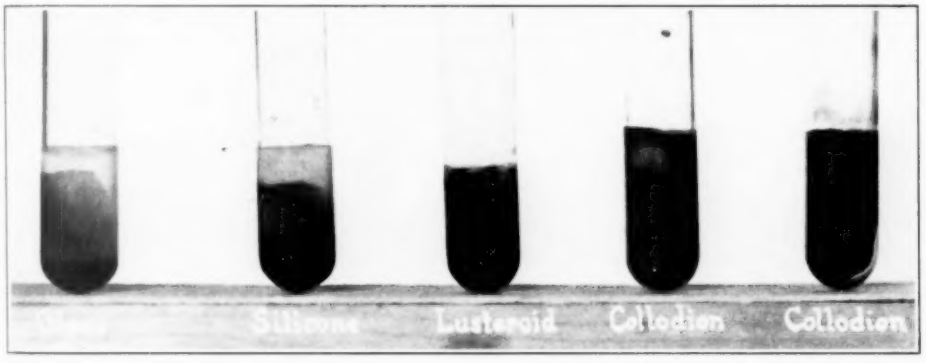


FIG. 3.—The Effect of the Surface of the Container on Clot Retraction.
Retraction is poor in lusteroid and absent in the collodion coated tube. When additional thrombin is supplied, some retraction occurs in collodion tube, as seen in Tube 5.

4, the cell volume of the blood. The first two are intrinsic, whereas the remaining ones are extrinsic. There are probably other minor factors such as the concentration of fibrinogen. It is fairly certain, however, that this substance plays essentially a passive role, and that the usual range of concentration has no significant influence on retraction.

Recently Ackroyd[2] observed that when he added sedormid to the blood of patients who had recovered from thrombocytopenic purpura induced by this drug, platelet agglutination and lysis rapidly occurred, and no clot retraction took place. This can be considered as further proof that clot retraction is caused only by intact and discrete platelets.

THE PHYSIOLOGICAL FUNCTION OF CLOT RETRACTION. *Hemostasis.* As long as the fibrin clot was looked upon as a mechanical plug which the organism employed to effect stanching, it was logical to assign to retraction a specific role in this mechanism. Frank[7] believed that it functioned in closing injured vessels, and Fonio[5] designated retraction as a physiological ligature. Quick[24] in his monograph showed by means of a pen drawing how retraction could theoretically pull in the torn edges of a severed vessel. This idea was accepted by Seegers and Sharp[32], and by Aggler and Lucia[3], who reproduced the drawing in color. Zucker[35], however, called attention to the fact that when an injured vessel was observed under the microscope, only platelet agglutination and vascular contraction was seen.

Clot retraction as a mechanical mechanism in hemostasis has no experimental confirmation, and there are obvious reasons why it is unlikely to have any role. In the first place, retraction is a slow process. In a test tube, it usually takes 30 minutes or more before any separation of serum can be observed. In the second place, the retractile force is so weak that it is inconceivable how it can pull arterial walls together against the force of the blood pressure. According to the theory of Quick[27], hemostasis is effected primarily by the liberation of a vasoconstrictor principle from disintegrating platelets. A clot within the lumen of a vessel need not be postulated. In fact, hemostasis can satisfactorily be explained by an extravascular clot which acts as the medium for the continuous slow production of thrombin which in turn causes the disintegration of platelets and an uninterrupted lib

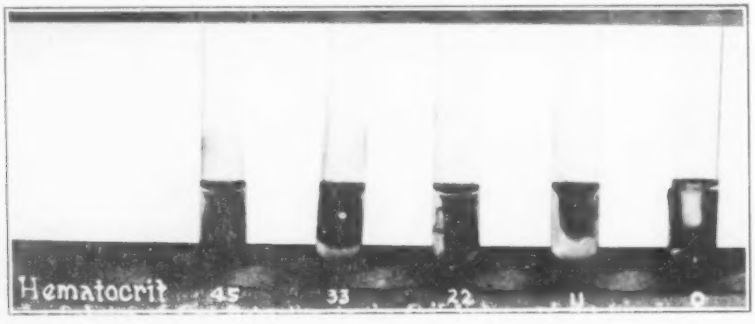
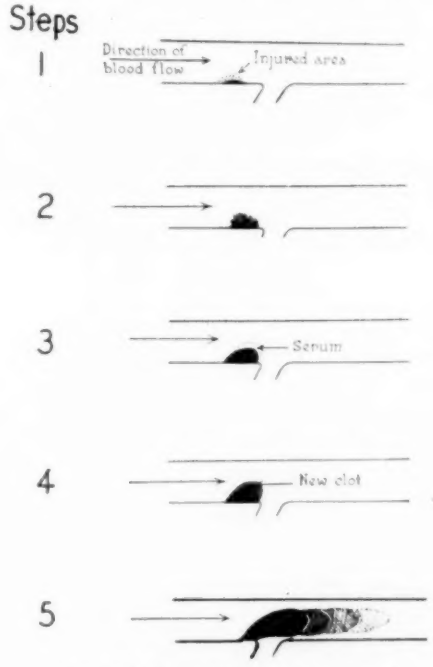


FIG. 4.—The Relation of Clot Retraction to the Cell Volume of the Blood.
The composition of the plasma and the platelet count were maintained constant, but the red cell volume was varied.

eration of the vasoconstrictor agent (thrombotonin). The clot must not be regarded as an inert end-product of the coagulation mechanism, but rather as the medium for the continuation of the process.

Venous Thrombosis. Surprisingly few investigators have considered a possible relationship between clot retraction and thrombo-embolism. Lampert[17] in 1935 assigned a probable role to clot retraction in the mechanism of thrombosis. Hirschboeck and Coffey[14] observed that clot retraction time was shortened in patients that had recent pulmonary embolism. Hirschboeck[13] extended these studies and devoloped a simple test for determining clot retraction. The procedure consists in timing the appearance of a globule of serum after a drop of blood has been suspended in castor oil.

When Quick and Favre-Gilly[29] discovered that very little prothrombin was converted to thrombin in the unretracted clot, but that a rapid conversion ensued when the clot was mechanically separated from the serum by centrifugation, it became clear that the serum expressed by retraction likewise was rich in nascent thrombin. This offered a logical explanation for the propagation of a thrombus in a vessel. The various steps in the process are presented in Fig. 5. As a result of an injury to the vessel wall, even though it be minor, the endothelial surface becomes altered. Platelets re-



IG. 5.—The Probable Sequence in the Formation of a Venous Thrombus.
Step 1. Injury of vessel wall, adherence of platelets to local area of trauma.
Step 2. Disintegration of platelets. Formation of a reticulated fibrin clot enmeshing intect latelets.
Step 3. Retraction of primary clot expressing a serum rich in nascent thrombin.
Step 4. Formation of a new fibrin coagulum attached to the primary thrombus.
Step 5. Growth of thrombus by successive formation of new clots, repeated elaboration nascent thrombin by clot retraction.

pelled by normal endothelium begin to adhere to the damaged intima. Soon the traumatized area is covered by agglutinated platelets. As these cells disintegrate, thrombin is formed which produces a fibrin clot attached to the vessel wall. As this primary clot undergoes retraction, it expresses a serum in which thrombin will quickly form. If the circulation is rapid, the serum is promptly washed away. This is what occurs in an artery as a rule and explains why arterial thrombosis is rare.

In a vein, especially if the circulation is sluggish, the expressed serum causes the coagulation of the blood about the primary thrombus. A new coagulum is thus superimposed and attached to the initial clot. The new portion of the thrombus has intact platelets enmeshed in its reticulum; therefore, it will undergo retraction, a fresh serum will exude and a new clot will form. Thus by successive retractions, the thrombus grows. The propagation of the clot will be in the direction of the blood stream, and will occur mostly at the tip. A long thrombus, unattached except at the area of origin, can form and it will float freely in the vein, since retraction reduces its diameter to less than that of the lumen.

If the concept relating clot retraction to venous thrombosis is correct, the factors that influence retraction should likewise be factors in thrombosis. As already stated, 4 major factors affect clot retraction. The first is the number of circulating platelets. It is well known that thrombocytosis predisposes to thrombosis and embolism. Thrombosis is not uncommon following splenectomy, and after this operation a marked rise in platelets usually occurs.

In regard to the second factor, increase in thrombin production, positive proof is lacking, since no good methods have been available to measure changes in thrombin formation. With the new prothrombin consumption test[25,26], it is probable that a relationship may be established. Hyperprothrombinemia has no practical significance, as even a normal concentration of prothrombin exceeds the supply of available thromboplastin. It is the latter agent which is the limiting factor in coagulation, and preliminary studies show that it fluctuates widely even in normal individuals. Its measurement by the prothrombin consumption test offers a promising approach, at least theoretically, to the detection of a thrombotic tendency. At present reduction of thrombin formation is used successfully in reducing the incidence of thrombosis. Both heparin and Dicumarol decrease the formation of thrombin. Heparin is both an antithrombin and an antiprothrombin, whereas Dicumarol causes a fall in the level of the prothrombin in the blood.

The third factor, the surface surrounding the clot, offers an explanation for the difference in the tendency to embolism between thrombophlebitis and phlebothrombosis. If a large section of the vein becomes inflamed, platelets will adhere over an extensive surface. The resulting clot, therefore, is firmly attached and pulmonary embolism is rare. Recurrent thrombophlebitis or thrombophlebitis migrans is a good example of a pure inflammatory type. The more pronounced the symptoms, the more extensive the inflammation and the firmer the attachment of the clot. In the phlebothrombotic type, the area of impaired vein wall is small and the intima surrounding the clot is normal. Therefore, a clot 12 to 18 inches in length may float freely with no attachments along its course in a vein.

The influence of the cell volume of the blood on clot retraction is fairly

well known, but the relation of anemia to thrombosis is often overlooked. Shaw in 1924 discussing a paper of Glynn[9] on thrombosis stressed the importance of anemia in thrombo-embolism; Dr. Donald, the chairman of the meeting, agreed with Shaw's views. Ochsner[21] also named anemia as a factor in thrombosis, but he attributed the tendency to a diminution of cardiac tone. Hirschboeck[13] called attention to anemia as a cause of increased clot retraction, and a factor in thrombosis. In the present study the relationship of cell volume to clot retraction is again demonstrated experimentally. The increased retraction of anemic blood may be enough to produce a thrombotic tendency, even though the other factors remain unaltered. According to this view, transfusions to correct anemia become an important prophylactic measure.

Summary. Clot retraction was studied to determine its probable function in hemostasis and venous thrombosis. The reasons are discussed why it is unlikely that the organism employs the retraction of the clot as a mechanical means of effecting stanching of blood.

The possible role of clot retraction in thrombosis is presented. The initial clot, formed as the result of vascular damage which causes platelets to accumulate and disintegrate, on contraction expresses a serum rich in nascent thrombin. If the circulation is sluggish the formation of a secondary clot about and attached to the primary coagulum occurs. By successive formation and retraction of the new clots, the thrombus is propagated. According to this concept, the factors which increase clot retraction should increase a tendency to thrombosis. With this objective the primary factors causing retraction were investigated.

A rise in the platelet count causes augmentation of retraction and clinically it is known to increase the thrombosing tendency. Conditions which bring about an accelerated formation of thrombin cause faster and greater clot retraction. It may be postulated that it also increases the incidence of thrombo-embolism. By reducing the formation of thrombin, the tendency toward thrombosis is depressed. This is clinically accomplished by means of heparin and Dicumarol. The inability of a fibrin clot to adhere to a non-wettable surface explains why an intravascular clot forms little or no attachments to healthy normal intima. Total blood cell volume is an important determinant of clot retraction.

In severe anemia retraction is both rapid and marked in extent. This suggests that anemia is a significant contributory factor in thrombosis and embolism, a fact verified by clinical observation. The importance of blood transfusion to correct anemia as a prophylactic measure against thromboembolism is stressed.

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TREATMENT OF POTASSIUM RETENTION IN ANURIA WITH CATION EXCHANGE RESIN*

A PRELIMINARY REPORT

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The progressive development of an elevated concentration of potassium in extracellular fluid, with resultant cardiotoxicity, has been recognized as one of the principal hazards in severe renal insufficiency associated with oliguria or anuria[6,8,15,16,20,25]. In the absence of adequate means for artificial dialysis, no reliable method has been available hitherto for the treatment of this complication. This paper is to report that such hyperkaliemia appears to be simply and effectively controlled by the enteral administration of cation exchange resin.

Cation exchange resins are synthetic polymers with sulfonic or carboxylic side chains which exchange hydrogen or ammonium ions for other cations. These resins have been demonstrated to take up sodium in the intestinal tract and have been found useful in the treatment of various types of edema[2,3,4,13,14,18]. Since potassium may also be removed from the body by such resins[3,13,14,18], their use in renal insufficiency complicated by hyperkaliemia seemed logical. For this reason the following studies were undertaken.

Experimental Material and Methods. A carboxylic ammonia exchange resin† was administered by mouth or by rectum to 3 oliguric or anuric patients with chronic or acute renal insufficiency who were developing hyperkaliemia. Patient J. R. was a 36 year old negro male with hypertensive cardiovascular disease and nephrosclerosis with chronic uremia and oliguria. Patient I. C. was a 43 year old white woman with lower nephron nephrosis and anuria due to an incompatible blood transfusion. Patient R. F. was a 40 year old white man with a similar

* This work was done in the Chemical and Renal Sections of the Department of Medicine and in the William Pepper Laboratory; the help of the several staffs is gratefully acknowledged. Laboratory facilities were aided by grants from the National Heart Institute, U.S.P.H.S., and by the C. Mahlon Kline Fund of the Department of Medicine.

† We are indebted to Smith, Kline and French Laboratories, Philadelphia, for supplying the ammonium form of the resin, Amberlite XE-96, used in these studies. This form of the resin contains no potassium and should not be confused with their preparation, Resodec, which is a mixture of both ammonium and potassium forms. The latter is contraindicated in hyperkaliemia.

condition. Resin was administered orally or by tube to Patient J. R. as a 7% suspension in whole milk or as a 17% suspension in water, respectively. Patient I. C. received the resin by enema as a 10% suspension in water, because she repeatedly vomited the resin when it was given by mouth. Patient R. F., therefore, was given resin by rectum to forestall possible emesis. The administration of resin in enemata had the further advantage that the amount of cation exchanged could be measured in the returns.

During the study in each patient, serum and blood were analyzed daily for electrolytes and urea nitrogen, and, except for the latter part of the study of J. R., complete balances were measured of chloride, sodium, potassium and nitrogen. Sodium and potassium in serum and urine were determined by means of a Barclay internal standard flame photometer[23], chloride in serum and urine by the methods of Eisenman[5] and Harvey[11], respectively. Total CO_2 content was measured in serum by the method of Van Slyke, and nitrogen in urine and feces by macrokjeldahl. Stools containing resin were digested as the whole specimen with concentrated nitric acid and the diluted filtrate poured through the flame photometer for the determination of sodium and potassium. Such analyses of fecal specimens were checked with chemical methods (uranyl zinc acetate for sodium and chloroplatinate for potassium§) and the results agreed within 4%.

From the changes in serum concentration and the balance of chloride, the change in extracellular fluid volume (as chloride space) was calculated[7]. Given this value the trans-

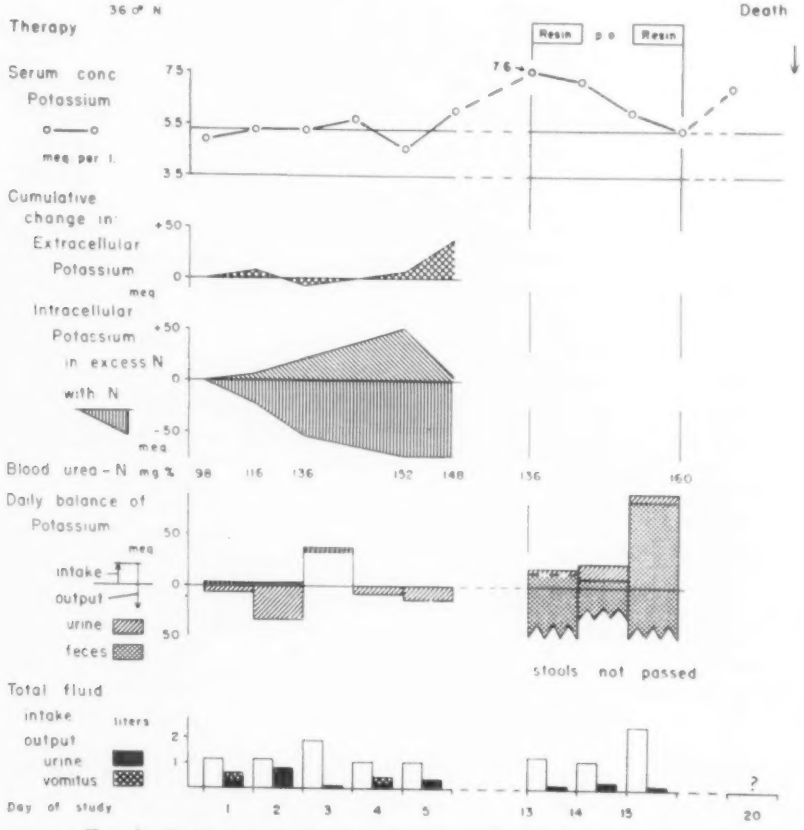

FIG. 1.—Patient J. R. Nephrosclerosis with oliguria and uremia.

§ Chemical analyses were done through the courtesy of Dr. A. E. Hemming of Smith, Kline and French Laboratories.

fers of potassium between extracellular and intracellular fluid were derived. The change in intracellular potassium was partitioned as that portion transferred as the result of tissue catabolism (or anabolism) and that moving in or out of viable cells, using a K:N ratio of 2.4 mEq. per gm. This partition requires a correction of the external nitrogen balance by multiplying the change in non-protein or urea nitrogen concentration of blood by an assumed total water volume, and hence is a rough approximation at best. However, these derived data, as charted in Figs. 1 to 3, give some picture of the internal transfers of potassium as affected by the experimental conditions.

Results. The results of the investigation are presented in Figs. 1 to 3 and in Table 1.

The course of Patient J. R. is presented in Fig. 1. It is seen that during an initial period of the oliguria the serum potassium concentration was slowly rising. The derived data indicate that this was the result of the breakdown of tissue with the release of potassium and an increased intake of the ion on Day 3, which increments were not retained in the cellular phase (Day 5). By Day 13 the serum concentration of potassium had reached 7.6 mEq. per liter. The ingestion of 50 gm. of resin on Days 13 and 15 were associated with a return of the serum potassium level to normal. Unfortunately, the amount of the ion removed could

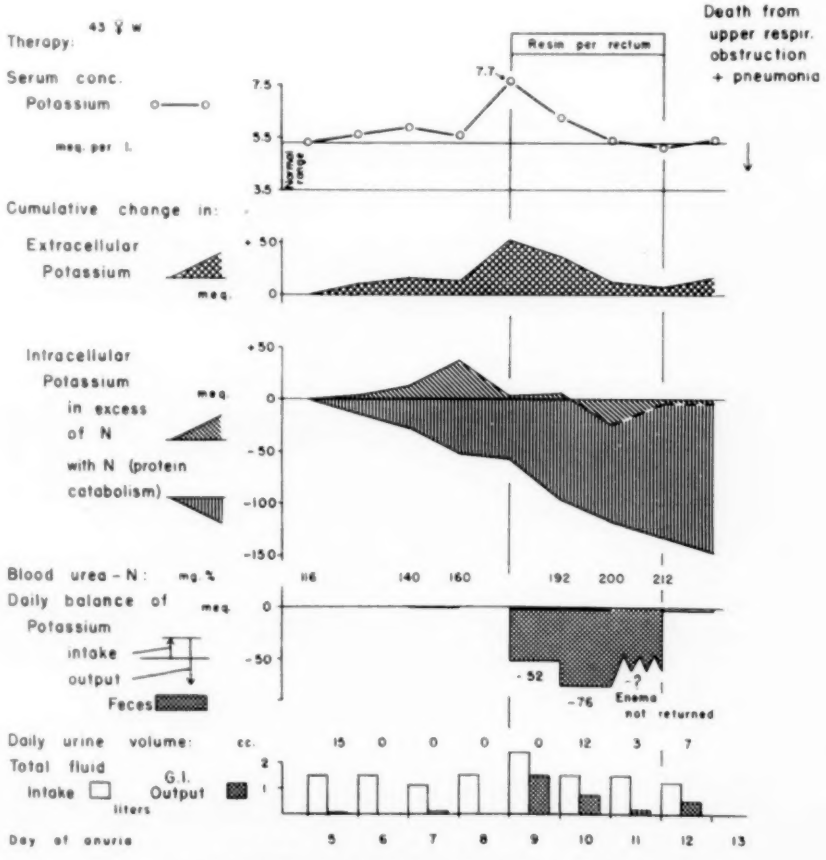

FIG. 2.—Patient I. C. Post-transfusion Anuria.

not be measured, as no stools were passed in this period or were collected later. After the succeeding 5 days without further administration the serum level became elevated and the patient died the next day.

In Patient I. C. (Fig. 2) the serum potassium concentration rose steadily and reached an elevation of 7.7 mEq. per liter on the 9th day of anuria. This rise appeared to be the result of a steady release of cellular potassium during catabolism and a failure of viable cells to take up the ion. When resin was administered by enema, an unexpectedly large amount of potassium was removed, mainly from the extracellular fluid, and the serum concentration fell to normal levels. Unfortunately the patient died of an unrelated complication before kidney function was restored.

In Patient R. F. (Fig. 3) the serum concentration of potassium rose from low normal to slightly elevated levels, apparently as the result of catabolism of tissue and failure of intact cells to take up potassium. On the 10th day of anuria resin enemata were begun. Despite an increased intake of potassium, these enemata resulted in a negative balance of the ion, mainly at the expense of the intracellular phase; the extracellular accumulation may have

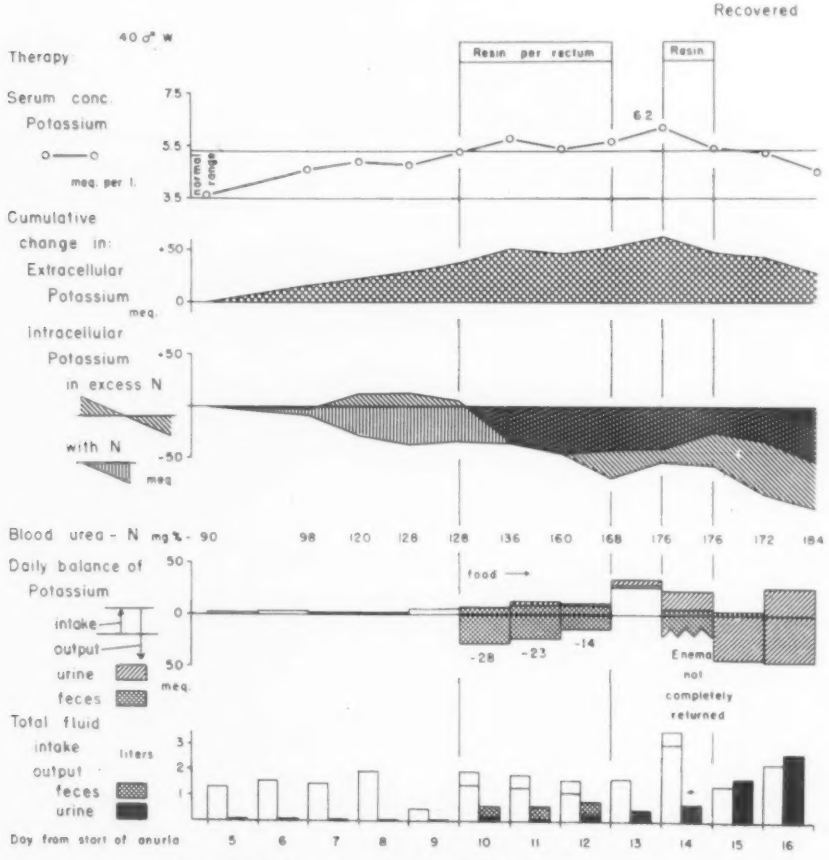

FIG. 3.—Patient R. F. Post-transfusion Anuria.

been retarded as well. The last resin enema coincided with the return of urine formation and the serum concentration fell as potassium was excreted by the kidney. The patient made an uneventful recovery.

In Table 1 is presented the evidence that significant amounts of potassium were removed by the resin enemata compared to normal stools not containing resin. The potassium removed ranged from 21 to 73 mEq. per liter per day, and always exceeded the amount of sodium obtained. Variability in the amount of cation removed must have been influenced to a large extent by variability in the length of time each enema was retained.

TABLE 1. DAILY POTASSIUM, SODIUM, AND CHLORIDE CONTENT OF STOOLS AND OF RETURNED RESIN ENEMATA*

Patient	*Type of specimen*	*Day after start of anuria*	*K mEq.*	*Na mEq.*	*Cl mEq.*	*N gm.*
R. F.	Normal stool	8	1	1	0	—
	Normal stool	9	1	1	0	—
	Resin enema	10	34	11	4	—
	Resin enema	11	31	9	6	—
	Resin enema	12	21	4	3	—
I. C.	Resin enema	9	49	29	10	3.3
	Resin enema	10	73	31	9	4.7

* Given as 10% suspension in water in volumes of 250 cc. twice daily. Retention varied from a few minutes to approximately 12 hours.

Discussion. In the 3 cases here reported the enteral administration of a cation exchange resin apparently mitigated the accumulation of potassium in extracellular fluid and the rise in serum concentration. Although the changes in the electrocardiogram consisted only of moderate elevation of the T waves and some lengthening of the Q-T interval, in 2 of the cases the serum potassium levels approached those which have been suspected of causing severe disturbances in cardiac function, namely 7.4 to 8.1 mEq. per liter[6,22]. The induction of a fall in serum potassium concentration from this vicinity, therefore, removed at least one factor threatening the survival of the patient.

Hyperkaliemia is not an uncommon occurrence in severe renal insufficiency associated with oliguria or anuria[6]. Low serum levels of potassium are sometimes observed in this situation but appear to be less frequent[6]. Where an elevated concentration threatens the patient, a number of measures, short of artificial dialysis, have been tried with indifferent success. These include the administration of a high carbohydrate intake plus insulin to promote the uptake of potassium by cells[1,6], and the use of calcium to antagonize the effect of potassium on the heart[8,10,20]. Artificial dialysis, of course, offers a sure method to remove potassium and lower the concentration in extracellular fluid. This has been demonstrated by use of the Kolff dialyser[17,21,24], and the other methods of small intestinal lavage[19] and peritoneal lavage[9] should be equally efficacious. Indeed, at the time of writing, hyperkaliemia is one of the few absolute indications for the use of artificial dialysis by those technically prepared. However, relatively few physicians have such facilities available, and most patients with acute anuria due to a reversible renal lesion can be brought through by careful con-

servative medical treatment. Such a regimen includes restriction of water intake to meet only the needs of extrarenal water loss, the preservation of the total electrolyte concentration of body fluids (as indicated by the sodium concentration) and the combatting of acidosis by the use of sodium bicarbonate or lactate, and a high caloric intake to minimize protein catabolism and release of potassium. The oral administration of aluminum hydroxide to mitigate the rise of the serum phosphorus level, the injection of calcium to prevent the onset of tetany during alkali therapy, and support of the circulation are important therapeutic adjuncts. Under such circumstances, the demonstrated efficacy of cation exchange resin in controlling the complication of hyperkaliemia should greatly facilitate the ordinary medical treatment of anuria.

The resin has not been found to be toxic to animals and man[12], but one adverse effect possibly occurred in Patient R. F. The removal of sodium by the resin may have produced a lowering of the serum sodium concentration with resultant augmentation of the acidosis. This effect was readily corrected by the administration of sodium bicarbonate, and therefore does not constitute a serious objection to the use of resin in this condition.

Summary and Conclusions. Cation exchange resin, given by mouth or by rectum, has been demonstrated to lower elevated serum potassium concentration in 3 patients with renal insufficiency and oliguria or anuria. When the resin is not tolerated in the upper gastrointestinal tract, it may be given as an enema and significant amounts of potassium ion removed by this route.

Additional experience since this report was submitted has emphasized the quantitative variability of potassium removed by enemas, and the desirability, whenever possible, of giving the resin by mouth for more reliable results.

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COLLOIDAL IRON: A WELL TOLERATED, EFFECTIVE ORAL HEMATINIC

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Treatment of the hypochromic microcytic anemias (the commonest of all the anemias) calls for iron in a form readily utilizable for hemoglobin production and in doses that are adequate. The necessity for adequate dosage is now well established, but in practice certain difficulties arise. It is generally agreed that anemia of the hypochromic, microcytic type is due to iron deficiency, and that in treatment the first objective is to eliminate the etiological fault, then administer iron. Such optimum iron therapy raises two problems: which iron preparation, and how much?

Many forms of iron and iron salts are in use. Blaud gained fame with his pills of ferrous carbonate; he was one of the first to stress the importance of large doses of iron. Bunge later caused iron therapy to fall in disrepute because of his erroneous calculation of iron dosage. Ferrous sulphate, iron and ammonium citrates, ferrous chloride, ferrous gluconate, and reduced iron have all had wide use. All have certain disadvantages. Ferrous salts and other commonly employed forms of iron produce gastrointestinal irritation of varying severity in a number of patients. The reported incidence of such symptoms runs as high as 33⅓%[1,2]. Nausea, vomiting, heartburn, diarrhea, and constipation are common complaints. The distress is usually proportional to the size of the dose. If maximal improvement is to be obtained, adequate dosage is essential. However, if one persists in ordering such doses of a poorly tolerated iron preparation the patient often abandons treatment. If the dose of such preparation is reduced to the "tolerance level", improvement is slow and uncertain. The answer to this common therapeutic dilemma would seem to be a form of iron which is effective, yet one which causes little or no gastrointestinal irritation.

Over the past 10 years, clinical trials with various iron preparations have been conducted in the Hematology Section of the Medical Clinic of the Hospital of the University of Pennsylvania. Certain patients with known intolerance for various iron preparations have served as screening subjects. One product has emerged as a potent yet well tolerated form of iron. This is a preparation of *colloidal* iron combined with or dispersed in a colloid made by the digestive action of papain on casein. This compound contains 20% of iron.*

The product is stable and generally non-irritating, and is suitable for administration in uncoated compressed tablets or in capsules which disintegrate rapidly so that absorption may occur in the stomach. This is of great importance because Hahn *et al.*[4],

* This preparation, Ferrocol®, was supplied by the Mulford Colloid Laboratories, Philadelphia.

using radioactive iron, have shown that iron is absorbed principally from the stomach and upper intestinal tract.

The drug was prescribed in doses of 0.3 gm. of the colloidal iron compound; the usual total daily dose was 1.2 gm. (4 capsules per day providing 240 mg. of actual iron). Following elevation of hemoglobin to satisfactory levels a maintenance dose was usually prescribed. The patient was instructed to take the colloidal iron compound in the regular or slightly reduced dosage for 1 week each month. This maintenance program is of great benefit to women during the menstrual years of life because of the frequently excessive loss of iron with the menstrual flow, to patients whose diets are presumably substandard in iron intake, and during pregnancy with its increased iron requirements.

To test the efficacy of this drug it was given to a group of 25 patients with chronic hypochromic microcytic anemia. All blood counts and hemoglobin determinations were made by the same technician. Certified pipettes were used for the red cell counts; hemoglobin determinations were made photoelectrically. The patients in this group were unselected; they were representative of those normally seen in clinical practice. The average initial hemoglobin level of the group was 10.14 gm. per 100 cc. of blood (65%); it ranged from 8.0 gm. (51.5%) to 12.65 gm. (81%) (Table 1). There ensued a hemoglobin increase of such degree that the average gain over a period of 9 weeks was 2.56 gm. per 100 cc. of blood (16%). It is recognized that, other factors being equal, the rate of hemoglobin regeneration will depend upon the degree of anemia at the start of treatment. The anemia in this group of persons was not severe and a gain of 2.5 gm. during such a period is considered satisfactory[2].

Complete absence of symptoms of gastrointestinal intolerance to this preparation of colloidal iron emerged as an impressive fact in this group of patients. A second group was then selected especially to evaluate this aspect of the drug. This group of 23

TABLE 1.—EFFECT OF COLLOIDAL IRON COMPOUND ON HEMOGLOBIN FORMATION

Case No.	Diagnosis	Initial hemoglobin		Daily dose colloidal iron comp.	Duration of treatment	Final hemoglobin		Hemoglobin increase	
		%*	Grams	Grams	Weeks	%*	Grams	%*	Grams
1	Antepartum; food allergy	63	9.8	1.2	5	76	11.8	13	2.0
2	Chronic menorrhagia	59	9.2	1.2	10	86	13.4	27	4.2
3	Nutritional and post-infection anemia	76	11.9	1.2	12	91	14.1	15	2.2
4	Cardiac failure; hypertension	70	10.9	1.2	8	87	13.5	17	2.6
5	Malnutrition; bleeding hemorrhoids	63	9.8	1.2	8	83	12.9	20	3.1
6	Non-toxic nodular goiter; tonsillectomy	75	11.6	1.2	6	85	13.3	10	1.7
7	Chronic cholecystitis	65	10.1	1.2	13	84	13.1	19	3.0
8	Acute bronchitis; tonsillitis	65	10.1	1.2	3	75	11.6	10	1.5
9	Esophageal dilatation due to achalasia; nutritional anemia	81	12.6	1.2	9	88	13.7	7	1.1
10	Antepartum	65	10.1	1.8	4	75	11.7	10	1.6
11	Antepartum; mild toxemia	54	8.4	1.8	9	66	10.3	12	1.9
12	Functional gastrointestinal disease	65	10.1	1.2	16	81	12.6	16	2.5
13	Hypertension; post-menopausal vaginal bleeding	71	11.1	1.2	6	84	13.1	13	2.0
14	Antepartum	56	8.7	1.2	5	72	11.2	16	2.5
15	Antepartum	54	8.4	1.2	6	76	11.8	22	3.4
16	Antepartum	56	8.7	0.9	7	75	11.7	19	3.0
17	Antepartum	52	8.0	0.9	9	64	9.9	12	1.9
18	Antepartum	76	11.8	1.2	10	85	13.3	9	2.5
19	Antepartum	66	10.2	1.2	20	80	12.5	14	2.3
20	Antepartum; latent syphilis	52	8.0	1.2	8	67	10.5	15	2.5
21	Antepartum	63	9.8	1.2	18	84	13.1	21	3.3
22	Mild nutritional anemia	78	12.1	1.2	10	94	14.7	16	2.6
23	Chronic blood loss	66	10.3	1.2	14	86	13.3	20	3.0
24	Chronic menorrhagia; hysterectomy	79	12.2	0.9	7	99	15.4	20	3.2
25	Arteriosclerotic heart disease	57	8.9	1.2	5	86	13.5	29	4.6
	Average	65	10.14		9	81	12.6	16	2.56

* 15.6 gm. Hemoglobin per 100 cc. blood = 100%

consisted mainly of patients from the Prenatal Clinic; such women often show heightened irritability and other abnormalities of gastric function. Furthermore, all of the patients chosen for testing had been unable to take ferrous sulfate or ferrous gluconate without experiencing discomfort of one type or another; indeed several had refused to continue iron medication for this reason.

occasional symptoms of intolerance might be found. It is nevertheless significant that, in a group selected because of demonstrated intolerance to one or more of the other iron preparations, similar symptoms did not occur in any patient after ingestion of the colloidal iron compound. While the psychological factor may be important in certain individuals exhibiting apparent intolerance to iron

TABLE 2.—TOLERANCE STUDY

Case No.	*Diagnosis*	*Intolerance shown to*	*Previous symptoms of intolerance*	*Daily dose colloidal iron comp.—Gm.*	*Duration of treatment Days*	*Symptoms of intolerance of colloidal iron compound*
26	Antepartum	Ferrous sulfate	Vomiting	1.2	114	None
27	"	"	Nausea	1.2	14	"
28	"	"	Nausea and constipation	1.2	12	"
29	Chronic hypochromic anemia (nutritional)	Ferrous gluconate	Diarrhea	0.6	90	"
30	Antepartum	Ferrous sulfate	Nausea	3.0	56	"
31	"	"	Vomiting	1.8	122	"
32	"	"	Vomiting	1.8	28	"
33	"	"	Vomiting	1.8	160	"
34	"	"	Severe nausea and vomiting	1.8	21	"
35	"	"	Persistent nausea	1.8	135	"
36	"	"	Abdominal cramps	1.8	83	"
37	"	"	Nausea	1.8	35	"
38	"	"	Abdominal cramps	1.8	120	"
39	"	"	Nausea	1.8	154	"
40	"	"	Constipation and nausea	1.2	133	"
41	"	"	Nausea and vomiting	1.2	20	"
42	"	"	Nausea and vomiting	1.2	54	"
43	Antepartum; pyelitis	"	Nausea and vomiting	0.9	42	"
44	Pyelonephritis; right nephrectomy	"	Abdominal cramps	1.8	210	"
45	Tertiary syphilis	"	Tinnitus	1.2	63	"
46	Antepartum	"	Vomiting	1.8	45	"
47	Chronic menorrhagia	Ferrous gluconate	Gastrointestinal distress	1.2	70	"
48	Nutritional and post-infection anemia	"	Nausea	1.2	84	"

The findings in this "intolerant" group were convincing (Table 2). All were able to tolerate this colloidal iron preparation in therapeutic doses without any evidence of gastrointestinal irritation. It was repeatedly observed that patients wary of anti-anemic therapy because of distress from other hematinics, reported no symptoms of irritation after taking full doses of the colloidal iron compound. Not a single instance of inability to tolerate the preparation was encountered, nor was even mild discomfort reported. It is recognized that the number of cases is small and that in a larger group medication, every effort was made to convey no pre-treatment suggestion to this group of patients.

Summary. 1. A clinical evaluation of a colloidal iron compound was performed.

2. This compound has proved to be a satisfactory source of iron for hemoglobin regeneration in iron deficiency anemia.

3. Of great practical importance is the fact that full therapeutic doses did not produce distressing gastrointestinal symptoms during pregnancy, and in patients who had been intolerant of other forms of iron.

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INCONCLUSIVE RESULTS OF PARATHORMONE TREATMENT FOR ESSENTIAL THROMBOPENIC PURPURA

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The possible value of parathyroid hormone in the treatment of essential thrombopenic purpura was suggested in the reports of Lowenburg and Ginsburg[2,3]. They noted an apparent clinical and hematologic response in 2 patients following the induction of an acute hypercalcemia with parathormone. The first patient treated similarly at the Cleveland Clinic seemed to show a prompt and permanent recovery following an induced hypercalcemia with parathyroid extract after splenectomy had been of no demonstrable value[1]. This experience led to a clinical trial of parathyroid hormone in like conditions.

This report presents an analysis of 27 cases of essential thrombopenic purpura (Werlhof's disease) treated with parathyroid hormone to determine the therapeutic value of the agent. The cases selected had adequate clinical data and follow-up reports. Patients with purpura resulting from allergy, drugs, hepatic or renal insufficiency, or primary blood dyscrasias have been excluded.

Procedure. Prior to the administration of parathyroid hormone, the following studies were performed: complete hemogram, platelet count, bleeding time, coagulation time, marrow study by sternal aspiration. Control serum calcium and phosphorus were determined. The patients were given subcutaneous or intramuscular injections of parathormone, 100 to 200 units, every 4 to 6 hours for several days. The blood calcium and phosphorus levels were determined daily together with the platelet count. In children, smaller doses such as 100 to 200 units daily were usually sufficient to produce a significant hypercalcemia within 48 hours. Several patients received more than one course of parathormone therapy.

Results. Improvement was measured by prompt clinical response, appreciable rise of the platelet count, and a decrease of the bleeding time within 48 hours following the course of parathormone injections. Of the 27 patients, 10 were classified as having obtained a good result according to these criteria. Follow-up studies indicate that none of these 10 patients has shown evidence of clinical recurrence of purpura. Fifteen patients in this group failed to show any definite improvement during or immediately after parathormone administration. Equivocal results were noted in 2 patients. In one of the patients who showed an equivocal response, there was a prompt clinical recovery with each of 2 courses of parathyroid hormone but a subsequent relapse with purpuric phenomena occurred. The second patient, in whom splenectomy had been performed 5 years previously, obtained a prompt remission for 8 weeks but failed to respond to a second course of parathormone and subsequently died of a cerebral hemorrhage (Table 1).

TABLE 1.—RESULTS OF TREATMENT WITH PARATHORMONE IN 27 PATIENTS

Age group	*Good*	*Poor*	*Equivocal*	*Total*
3–14 inclusive	5	3	1	9
15–37	2	8	1	11
37–68	3	4	–	7
Total	10	15	2	27

There is an insufficient number of patients in various age groups (Table

1) to make the results statistically significant. There seems little doubt, however, that the failures are conspicuous in the 15 to 37 age group in which only 2 of 11 patients showed any definite improvement. There are 4 patients in this series who failed to obtain a permanent recovery following splenectomy. Three of these also failed to respond to parathormone treatment following splenectomy (Table 2). Of

TABLE 2.—PARATHORMONE TREATMENT WITH SPLEEN PRESENT

	Good	*Poor*	*Equivocal*	*Total*
Spleen present	9	12	2	23
Spleen absent	1	3	–	4
Total	10	15	2	27

the 7 patients in this age group (Table 3) who failed to respond to parathyroid, 5 recovered completely after subsequent splenectomy. The results obtained in the younger age group (3 to 11 years inclusive) and in the older age group (37 to 68 inclusive) appear to be somewhat better.

TABLE 3.—RESULTS OF SPLENECTOMY IN 11 OF THE 27 PATIENTS

Age group	*Good*	*Poor*	*Total*
3–14 inclusive	2	–	2
15–37 "	5	2	7
37–68 "	1	1	2
Total	8	3	11

Discussion. The clinical course of essential thrombopenic purpura is variable, so that the evaluation of any single form of therapy is difficult. In infants and children, this disease is often preceded by infection, and spontaneous recovery generally occurs within a few weeks in the majority. The diagnosis of essential thrombopenic purpura at older ages is sometimes questionable and often established only by exclusion of possible secondary causes for purpura. Because only 2 of the 11 patients in the 15 to 37 age group obtained an immediate and apparently satisfactory response to parathormone, this form of therapy appears to be of questionable benefit. Rosenthal[4] has noted a similar ineffectiveness in results obtained by parathyroid hormone.

There seems to be no rationale for the use of parathyroid extract in the treatment of essential thrombopenic purpura. Patients with this condition show no evidence of disturbance of calcium metabolism. The total serum calcium, ionized calcium, and serum phosphorus remain within normal limits. No evidence exists of appreciable alteration of the serum proteins to which part of the calcium is bound. The role of diffusible or ionized calcium in capillary permeability appears significant. Zweifach's[5] direct observations of the capillaries of the frog mesentery indicate that by increasing the ionized calcium of the perfusate an increase of the intercellular cement results, thereby rendering the capillaries less permeable. He concluded from these experiments that the permeability of a capillary membrane can be explained without taking into account the cellular components of the vessels. Theoretically, the increased ionized serum calcium following parathormone treatment may render the capillaries less permeable and so decrease the purpuric manifestations.

Summary and Conclusions. The results obtained in 27 patients with essential thrombopenic purpura treated with parathyroid extract indicate that such therapy is of dubious value. Splenectomy appears to be followed by better results in this disease than does parathormone treatment.

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ACUTE BARBITURATE POISONING
ANALYSIS AND EVALUATION OF CURRENT THERAPY

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THE fact that aliphatic narcotics and central stimulants as exemplified by picrotoxin are mutually antagonistic in animals was discovered 75 years ago by J. Crichton Browne[6]. His observations were confirmed by a number of investigators, both as to the life-saving and awakening effects of central stimulants in chloral hydrate and paraldehyde anesthesia.

Maloney, Fitch, and Tatum[35], and Maloney and Tatum[34] were apparently the first to test the antidotal efficacy of picrotoxin in experimental barbiturate poisoning. The fact that barbiturates are the most widely employed hypnotics and basal anesthetics makes their findings particularly important. They found that picrotoxin shortens the recovery from barbiturate anesthesia and that it protects animals receiving doses higher than the LD_{50} of the various barbiturates. Koppanyi and his associates[28,39] explored the limits of the antidotal efficacy of picrotoxin, metrazol, and other analeptics in poisoning with barbituric acid derivatives, determined the component factors of the antidotal mechanism and provided a rational explanation of both the awakening and life-saving effects of these antidotes in experimental barbiturate intoxication. They also introduced picrotoxin and metrazol as effective agents for the treatment of human barbiturate poisoning. Few, if any, critical or adverse reports were published, and subsequently picrotoxin was introduced into the U.S.P.

In experimental barbiturate poison-

ing the usefulness of picrotoxin and metrazol is without question; for in these experiments the fatal doses of the various barbiturates can be accurately determined and the efficacy of the antidote can be accurately estimated by the determination of the number of fatal doses of barbiturates that can be antagonized by suitable doses of picrotoxin and metrazol. Unfortunately in the human population such exact data are not possible. We are dependent upon rough estimates gathered mainly from data reporting the fate of untreated cases of barbiturate poisoning when the doses ingested were known. These data are, of course, subject to many errors. The dose-body-weight relationship is practically never taken into consideration, the amount of barbiturate removed from the alimentary tract by gastric lavage or by catharsis is seldom determined, and the data obtained are often vitiated by the fact that the victim may also have taken liquor or various other drugs that may have enhanced or antagonized the effect of barbiturates. Furthermore, the calculation of the fatal human dose is almost entirely based on history, such as the presence of an empty bottle containing sodium amytal capsules in the room of the suicidal candidate. We do not know if the patient has taken all the capsules at once or over a period of hours, allowing at least some time for the elimination of the particular barbiturate. These possible sources of error may perhaps explain why there is such a great discrepancy between the oral fatal doses reported for different barbiturates in man and in several species of animals and why so many drugs are reported to be "effective" in the treatment of barbiturate poisoning. Eckenhoff *et al.*[15] in a report on analeptics concluded that: "Before the true part played by these drugs (analeptics) in the treatment of depression can be fully evaluated, more complete and detailed summaries must be made and compiled."

The purpose of this study is to compile such summaries and analyze the cases of barbiturate poisoning published in recent years[1-5,7,9,10,14,16,18,19,25,29,32,36,37,40,43-49,52] and to ascertain whether or not the treatment with the various analeptics actually had life-saving value or if recovery would have occurred even without specific treatment. The difficulties that may be encountered have already been indicated, and it is by no means easy to arrive at clear-cut conclusions such as those to which we are accustomed in experimental research.

Methods. Only one liberty was taken in treating the data to be presented, namely, the estimation of body weight of the patient when not reported. Arbitrarily, in the absence of specific data, we have assigned a weight of 70 kg. to an adult male and 60 kg. to an adult female. The concentration of the barbiturates ingested is expressed both in terms of total dose (gm.) and also as mg. per kg. of body weight. We have analyzed separately cases of poisoning with: a) barbital; b) phenobarbital; c) amytal; d) pentobarbital; e) seconal; and f) mixtures of barbiturates. Pulmonary complications, non-specific medication, the employment of chemotherapeutic agents, the age and sex of the patients and the results of the treatment were duly noted and tabulated. The efficiency of the analeptic agents (picrotoxin, metrazol, amphetamine, and succinate) was judged on the basis of the estimated oral fatal doses reported for man and the established oral LD_{50} for various experimental animals.

Barbital. In Table 1, 14 cases of barbital intoxication are reviewed. The 8 patients who recovered ingested from 180 to 300 mg. per kg. The 6 patients who succumbed (where the dose could be approximated) ingested from 83 to 464 mg. per kg. In 3 of the patients, caffeine with sodium benzoate was

the analeptic of choice; 2 received disodium succinate; and the remaining 9, picrotoxin. Two of the 3 patients who received caffeine died. Patient 7 who ingested 114 mg. per kg. of barbital and succumbed 20 minutes after admission certainly cannot be considered a therapeutic failure, as he was moribund when first seen. Patient 1 survived despite a dose of 300 mg. per kg. and hyperpyrexia. He received 0.5 gm. of caffeine with sodium benzoate q. 4 hours and camphor in oil on various occasions. Patient 12 also received caffeine and developed hyperpyrexia but succumbed 36 hours after admission. Patients 13 and 14, who ingested 118 and 156 mg. per kg. of barbital, were given disodium succinate and recovered. Five of the 9 patients who received picrotoxin recovered. All of the 4 patients who succumbed had pulmonary complications, and in each case the patient had been in coma for some time before analeptic therapy was instituted. It should be pointed out that Patient 2 who ingested the largest dose of barbital (464 mg. per kg.) and received the largest dose of picrotoxin recovered from his barbiturate coma but died subsequently of pneumonia and hepatitis.

Comment. The average oral dose of barbital for humans according to Hambourger[21] is 85 mg. per kg., while the LD_{50} for animals is about 300 mg. per kg. In view of the fact that all patients received some form of therapy, it is difficult to estimate the average oral fatal dose of the drug from our data. Patient 7 who received caffeine for only 20 minutes prior to death ingested only 114 mg. per kg., while Patient 1, who ingested 300 mg. per kg. and received caffeine at 4-hourly intervals, survived. Five of the patients who ingested concentrations of barbital significantly above 114 mg. per kg. survived with treatment.

The concentration of picrotoxin used in these cases was well above the convulsive dose of this drug, indicating that the depression resulting from the barbiturate was quite marked. The

TABLE 1. REVIEW OF CASES WITH BARBITAL INTOXICATION

			Dose			
No.	*Sex*	*Age*	*gm.*	*Mg./Kg.*	*Treatment*	*Result*
1	M	22	18.0	300.00	Caffeine—0.5 gm. q 4 h. Camphor in oil	Recovered. (Temperature 107° F.)
2	M	57	32.5	464.28	Picrotoxin—2134 mg.	Recovered from barbital. Died subsequently of pneumonia and hepatitis.
3	F	48	16.3 +Alcohol	271.67	Picrotoxin—1079 mg. Metrazol—1 Gm. following picrotoxin	Recovered.
4	F	39	16.4	273.33	Picrotoxin—314 mg.	Recovered.
5	M	37	12.0	171.43	Picrotoxin—?	Recovered.
6	M	21	10.0	142.86	Picrotoxin—?	Recovered. (Picrotoxin 12 hrs. after adm.)
7	M	young	8.0	114.00	Caffeine sodium benzoate and coramine	Died 20 min. after adm. (Pulm. stasis, failing resp.)
8	F	44	5.0	83.33	Picrotoxin—400 mg. (24 hrs. later)	Died. Pulm. edema on adm. Return of corneal reflex only response to therapy.
9	F	40	6.5	108.33	Picrotoxin—90 mg.	Recovered.
10	F	63	Unknown		Picrotoxin—60 mg.	Died 4 hrs. after adm. Pulm. edema and cyanosis.
11	F	24	Unknown		Picrotoxin—879 mg.	Died 12 days later in deep coma. First seen 24 hrs. after adm.—out of coma 2 days—mult. pulm. abscesses developed.
12	F	22	Unknown		Caffeine, coramine, atropine	Died 36 hrs. after adm. Before death, temp. 105° and resp. 50.
13	M	64	8.3	118.00	Disodium succinate—30 gm. Picrotoxin—48 mg.	Recovered.
14	F	58	10.0	156.00	Disodium succinate—30 gm.	Recovered.

cases complicated by pulmonary stasis and infection can hardly be used to help establish the average oral fatal dose of this drug. If we accept the fact that Patient 1 survived a dose of 300 mg. per kg. (probably an exceptional case) and that the caffeine is not an effective analeptic and that the hyperpyrexia did not exert any life-saving effect, then in only 1 of the 14 cases herein reported can it be assumed that picrotoxin exerted a beneficial effect. It might also be inferred that the LD_{50} of 300 mg. per kg. for animals more nearly approximates the true fatal dose for humans. That such a conclusion would be erroneous is borne out by the following facts. In the first place, it is generally agreed that the human population is more sensitive to the influence of the various barbiturates than are animals, and, in addition, it is hardly likely that the fatal dose of barbital is higher than that for phenobarbital. It is well known from clinical and experimental experience that such is not the case and that much larger concentrations of barbital are required to produce a sedative action. We feel that the figure of 150 mg. per kg. more nearly represents the LD_{50} of barbital for humans (see Discussion). If such be the case, then one may conclude from these data that in 4 of the patients who recovered, picrotoxin exerted a life-saving effect.

PHENOBARBITAL. Fourteen cases of poisoning with phenobarbital are reviewed in Table 2. Of these 14, 8 survived, and the estimated ingested dose varied from 25 to 162 mg. per kg. The 6 patients who succumbed ingested from 67 to 176 mg. per kg. The 1 patient who did not receive analeptic therapy recovered from a dose of 40 mg. per kg. Of the 6 patients who succumbed, 5 received fairly large amounts of picrotoxin. The convulsive dose of picrotoxin for animals upon intra-

TABLE 2.—REVIEW OF CASES WITH PHENOBARBITAL INTOXICATION

			Dose			
No.	*Sex*	*Age*	*gm.*	*Mg./Kg.*	*Treatment*	*Result*
1	F	45	4.8	80.00	Picrotoxin—122 mg.	Recovered.
2	F	44	4.0	66.67	Picrotoxin—405 mg.	Died. On 6th day devel. pneumonia, never regained consciousness.
3	M	65	5.2	74.29	Picrotoxin—2154 m.	Died. Deep coma—24 hrs. Had pneumonia on adm. Died 8th day.
4	F	41	2.4	40.00	None	Recovered.
5	F	21	8.8	176.00	Picrotoxin—9 mg.	Died. Adm. 8 hrs. after ingestion, shallow resp., no more picrotoxin—died 22 hrs. after adm.
6	F	39	7.3	121.67	Picrotoxin—150 mg. Metrazol—1.2 mg. Atropine and conc. glucose	Died 16 hrs. after adm. Comatose, cyanotic rales. Temp. 105° and coma deepened. Pneumonia.
7	F	45	2.4	40.00	Picrotoxin—126 mg.	Recovered.
8	M	25	7.0	100.00	Picrotoxin—559 mg.	Recovered.
9	F	68	5.0	83.33	Picrotoxin—167 mg.	Died. First seen 36 hrs. later. Recovered enough to eat. Pneumonia and lung abscess.
10	F	23	3.0	50.00	Picrotoxin—720 mg.	Recovered.
11	F	24	6.5	103.33	Picrotoxin—5139 mg. Metrazol—1.43 gm.	Recovered.
12	F	48	7.0	116.67	Picrotoxin—1017 mg.	Died. Pneumonia, carcinoma with pulm. and vertebral metastases.
13	F	30	9.7	161.67	Picrotoxin—14,196 mg.	Recovered.
14	F	41	1.5	25.00	Amphetamine sulf.—100 mg. I.V. 6 hrs. (1.7 mg./kg.)	Recovered from semicomatose state.

venous injection has been estimated to be slightly higher than 0.5 mg. per kg. If this value applies to humans, then all but one of these patients received picrotoxin in concentrations well above the convulsive and probably fatal dose. It should be pointed out, however, that those patients who succumbed and developed pulmonary complications might have recovered had they received adequate concentrations of picrotoxin sooner.

Comment. According to the figures of Hambourger, the average oral fatal dose of phenobarbital for humans is approximately 140 mg. per kg. Studies on animals have revealed the oral LD_{50} to be from 150 to 175 mg. per kg. There appears to be unusually good agreement between these figures. The fact that Patient 2 ingested less than 70 mg. of phenobarbital per kg. and developed pneumonia on the 6th day without ever regaining consciousness certainly seems to indicate that Hambourger's figure of 140 mg. per kg. is too high and must be so since he assumes that 85 mg. per kg. of barbital is fatal. It is well known that phenobarbital is not only acutely twice as toxic as barbital but is also a longer-acting depressant (see Discussion). It is more in keeping with our present state of knowledge to assume that 75 mg. per kg. more nearly represents the true oral fatal dose for man. If this is so, then Patients 1, 8, 11, and 13 would have certainly expired without effective picrotoxin therapy.

Amphetamine was used in Case 14 following the ingestion of 25 mg. per kg. of phenobarbital, a dose which is routinely given for therapeutic purposes.

Mortality figures are extremely high both in this group and those ingesting

TABLE 3.—REVIEW OF CASES WITH AMYTAL INTOXICATION

No.	*Sex*	*Age*	*Dose*		*Treatment*	*Result*
			gm.	*Mg. Kg.*		
1	M	young	7.8	156.00	Picrotoxin—insignificant am't.	Recovered.
2	F	24	7.4	148.00	Picrotoxin—129 mg.	Recovered.
3	F	39	2.5	41.67	Picrotoxin—180 mg.	Recovered.
4	F	63	0.2	3.33	Caffeine Sodium Benzoate Picrotoxin—24 mg.	Recovered.
5	F	23	10.0	166.67	Picrotoxin—148 mg. Metrazol—1.8 gm.	Recovered.
6	F	24	8.0	133.33	Picrotoxin—30 mg.	Recovered.
7	F	20	1.2	24.00	Coramine—?	Recovered.
8	M	26	2.6	37.14	Picrotoxin—?	Recovered.
9	F	20	4.7	94.00	Picrotoxin—156 mg.	Recovered.
10	F	20	4.7	94.00	Picrotoxin—162 mg.	Recovered.
11	M	20	3.9	78.00	Picrotoxin—insignificant am't.	Recovered.
12	M	68	4.0	57.14	Picrotoxin—24 mg.	Recovered.
13	M	36	6.6	94.29	Metrazol—3.6 g.	Recovered.
14	M	38	4.0	57.00	Amphetamine sulfate—150 gm. I.V. in 8 hrs.	Recovered from deep coma.
15	M	45	4.0	57.00	Amphetamine sulfate—20 mg. I.V. q ½ hr. After 360 mg., pt. given caffeine, sod. benzoate, and ephedrine (Total—5.1 mg./kg.)	Died. Dev. pneumonia and died on 2nd day.
16	F	48	0.4	6.60	Disodium succinate—3 gm.	Recovered.
17			4.0	66.00	Metrazol—5.0 gm. Disodium succinate	Recovered.

barbital. The fatalities following the ingestion of these long-acting barbiturates were associated with a high incidence of pulmonary complications. Of the 28 patients who ingested either barbital or phenobarbital, 12 (43%) succumbed. In 10 (35%) of these cases, pulmonary complications were noted.

Pneumonia has long been recognized as a frequent complication of prolonged narcosis. Many of these patients developed pneumonia despite the prophylactic use of antibiotics. It may be worthwhile to point out that the majority of the patients who succumbed and developed pulmonary complications had been in comatose states for considerable periods of time. It is quite possible that the increased oxygen demand associated with fever and the added anoxia resulting from the decreased pulmonary reserve may have acted synergistically with the central depressant effect of the barbiturate and thus help explain the high increase of mortality when barbital depression and pneumonia co-exist.

AMYTAL. Seventeen cases of poisoning with amytal are presented in Table 3. The dose ingested varied from 3.33 to 167 mg. per kg. There was only one death reported—Patient 15 who ingested 57 mg. per kg. and received fairly large doses of amphetamine but succumbed on the 2nd day after having contracted pneumonia. All patients received some form of analeptic therapy. In 9 of the cases, picrotoxin was the agent of choice. In only 5 of these cases, however, was the concentration of picrotoxin used given in effective amounts. Patient 5 received picrotoxin and metrazol, and Patient 4, caffeine and picrotoxin. Two patients were given disodium succinate, and 2 received amphetamine. Patient 7 received an unknown concentration of coramine.

Comment. Hambourger's figure for the average human oral fatal dose of amytal is 23 mg. per kg. The oral LD_{50} for animals is about 110 mg. per kg. A review of these cases would seem to indicate that the value cited by Hambourger is far too low, if for no other reason than that such amounts have been used in humans to produce anesthesia (see Discussion). For example, Patient 11 ingested 78 mg. per kg. and recovered even though he received insignificant amounts of picrotoxin. On the other hand, if we accept the animal oral LD_{50} as applying to humans, which is unlikely, then Patients 2, 5, and 6 certainly recovered because of picrotoxin or metrazol therapy, and the same holds to a lesser extent for Patients 9, 10, and 13. One cannot conclude from the present data that either amphetamine or disodium succinate exerted a life-saving effect.

Amytal appears to be much better tolerated than does either barbital or phenobarbital. Since the urinary excretion of this compound is insignificant, its relatively rapid detoxification by the tissues offers a better prognosis. In view of its shorter duration of action, pulmonary complications are less frequently encountered.

It should be emphasized that the larger the dose of amytal and other immediate and short-acting barbiturates, the longer their duration of action. In other words, an exceptionally massive dose of amytal will produce as lasting a central depression as a moderately toxic dose of barbital or phenobarbital. Therefore, while specific analeptic therapy may not be indicated as frequently in intermediate or short-acting barbiturate poisoning as following barbital or phenobarbital intoxication, it is to be kept in mind that the consumption of the former drugs in very large quantities may produce a lasting depression requiring specific therapy.

PENTOBARBITAL SODIUM (NEMBUTAL). Nineteen cases of poisoning with nembutal are listed in Table 4. The estimated ingested dose varied from 13 to 150 mg. per kg. All the patients presented recovered, and all but one received analeptic therapy. The latter, Patient 7, ingested 11.67 mg. per kg. and, in addition, imbibed unknown concentration

of alcohol. He was given chloral hydrate to allay his excitement. Six of the patients were given amphetamine sulfate. The dose of nembutal ingested by the latter group varied from 13 to 24 mg. per kg. Patients 18 and 19, who received disodium succinate, consumed such relatively small amounts of nembutal (15 to 17 mg. per kg.) that one cannot, as with those receiving amphetamine sulfate, conclude that these substances exerted any life-saving effects. Picrotoxin was the analeptic of choice for 9 patients, and 1 patient received metrazol. These patients ingested from 17 to 150 mg. per kg. of nembutal. Nine of the 10 patients ingested a concentration greater than 45 mg. per kg.

Comment. The average oral human fatal dose of nembutal, according to Hambourger, is 14 mg. per kg., while for the large mammals it is stated to be 85 mg. per kg. The figure of 14 mg. per kg. is obviously too low for humans, and, since nembutal is acutely more toxic than amytal, it seems logical to conclude that all the patients who received picrotoxin, with the exception of Case 3, had consumed concentrations of this barbiturate greater than even our estimated fatal dose for

TABLE 4.—REVIEW OF CASES WITH PENTOBARBITAL SODIUM (NEMBUTAL) INTOXICATION

			Dose			
No.	*Sex*	*Age*	*gm.*	*Mg./Kg.*	*Treatment*	*Result*
1	F	28	6.0 +Alcohol	120.00	Picrotoxin—48 mg.	Recovered.
2	M	Late 50's	7.3	104.29	Picrotoxin—90 mg.	Recovered.
3	M	53	1.2	17.14	Picrotoxin—33 mg.	Recovered.
4	M	32	6.8	97.14	Picrotoxin—1944 mg.	Recovered.
5	F	35	8.0	133.33	Picrotoxin—308 mg. Sod. Phen. for convulsions	Recovered.
6	F	24	3.0	50.00	Picrotoxin—135 mg.	Recovered.
7	F	38	0.7 +Alcohol	11.67	Chloral hydrate by rectum to allay excitement	Recovered.
8	M	30	3.1	44.29	Picrotoxin—?	Recovered.
9	F	29	5.0	83.33	Metrazol—8.1 g.	Recovered.
10	F	27	9.0	150.00	Picrotoxin—insignificant amount	Recovered.
11	F	43	4.25	70.83	Picrotoxin—insignificant amount	Recovered.
12	F	23	1.5	24.00	Amphetamine sulfate—4 doses of 10 mg. I.V. in 5 hrs. (Total—0.7 mg./kg.)	Recovered. Seen 10 hrs. later—comatose, areflexic, cyanotic. After 40 mg. she talked and reflexes returned.
13	F	26	0.975	16.00	Amphetamine sulfate—4 doses of 20 mg. I.V. in 1½ hrs. (Total—1.3 mg./kg.)	Recovered. After 80 mg. patient responded.
14	F	23	1.46	24.00	Amphetamine sulfate—320 mg. in 7½ hrs. I.V. (5.3 mg./kg.)	Recovered despite coma and areflexic.
15	F	40	0.78	13.00	Amphetamine sulfate—40 mg. I.V.—1 dose (0.66 mg./kg.)	Recovered. In ½ hr. awoke from coma.
16	F	45	0.78 +Alcohol	13.00	Amphetamine sulfate—20 mg. I.V.—1 dose (0.33 mg./kg.)	Recovered ½ hr.
17	F	30	0.960 +Alcohol	16.00	Amphetamine sulfate—200 mg. I.V.—18 hrs. (3.3 mg./kg.)	Recovered.
18	F	66	0.9	15.00	Disodium succinate—4.5 gm.	Recovered.
19	F	38	1.0	16.6	Disodium succinate—6.0 gm.	Recovered.

TABLE 5.—REVIEW OF CASES WITH SECONAL INTOXICATION

No.	Sex	Age	Dose		Treatment	Result
			gm.	Mg./Kg.		
1	F	33	1.2	20.00	Picrotoxin—324 mg.	Recovered.
2	F	24	1.8	36.00	Metrazol—2.5 gm.	Recovered.
3	F	30	2.0	33.33	None	Died 15 hrs. after adm. Cematose 24 hrs. prior to adm. T. 108°. P. 160. R. 40.
4	M	49	0.75	10.71	Picrotoxin—24 mg.	Recovered.
5	F	32	5.8	96.67	Picrotoxin—926 mg.	Recovered.
6	M	45	1.5	21.43	Picrotoxin—?	Recovered.
7	F	43	1.0	16.60	Amphetamine sulf.—20 mg. I.V. q. ½ hr. (1½ mg./kg.)	Recovered after 90 mg. Recovered from coma, reflexes returned.
8	F	54	1.4	23.00	Amphetamine sulf.—210 mg. I.V. (3.5 mg./kg.)	Recovered.
9			4.6	65.00	Picrotoxin—585 mg.	Recovered.
10	F	23	1.3	21.30	Disodium succinate—42 gm.	Recovered.
11	M	63	1.8	25.70	Disodium succinate—27 gm.	Recovered.

TABLE 6.—REVIEW OF CASES WITH INTOXICATION FROM MIXTURES OF BARBITURATES

No.	Sex	Age	Mixture	Dose		Treatment	Result
				gm.	Mg./Kg.		
1	M	Mid. Age	Barbital	6.5	95.00	Picrotoxin—219 mg.	Recovered.
			Phenobarb.	3.3	41.00		
2	F	21	Amytal	5.0	83.00	Picrotoxin—669 mg. Repeated convulsions after picrotoxin, coramine, caffeine, and sucrose	Died 79.5 hrs. after adm. ? cerebral edema and anoxia—irreversible.
			Nembutal	1.29	20.00		
3	F	30	Amytal	5.2	86.00	Picrotoxin—60 mg.	Recovered.
			Phenobarb.	0.4	6.50		
4	F	17	Barbital	6.24	139.00	Picrotoxin—150 mg.	Recovered.
			Phenobarb.	1.56	34.00		
5	F	?	Barbital	4.72	78.60	Picrotoxin—60 mg.	Recovered.
			Phenobarb.	1.18	19.60		
6	F	35	Barbital	11.7	178.00	Picrotoxin—300 mg.	Died. Picrotoxin repeated several times. Striking return to consciousness after 2 hrs. Unconscious, picro. again, conscious, pneumonia, death.
			Phenobarb.	23.0	45.00		
7	F	35	Barbital	16.3	253.00	Picrotoxin—30 mg.	Died. Regained consciousness but died shortly thereafter. ? Rt.-sided failure p. m. Conscious 30 min.
			Phenobarb.	3.3	63.00		
8	F	32	Amytal	1.2	20.00	Picrotoxin—131 mg.	Recovered.
			Phenobarb.	4.9	20.00		
9	M	30	Barbital	6.5	95.00	Picrotoxin—228 mg.	Recovered.
			Nembutal	0.7	10.00		
10	F	22	Phenobarb.	?	?	Picrotoxin—373 mg.	Recovered.
			Seconal	2.0	40.00		
11	F	39	Seconal	1.5	25.00	Amphet. sulf.—400 mg. I.V. for 8 hrs.	Recovered from cematose state.
			Phenobarb. +Bromides	1.3	22.00		
				0.65			

humans (about 55 mg. per kg.). If such is the case, then Patients 1, 2, 4, 9, and 10 may well have recovered as a result of analeptic therapy.

It is interesting to note that all the patients recovered—again indicating that the short-acting barbiturates are definitely less dangerous for humans than the longer-acting ones, notwithstanding the contrary opinion expressed by Watts[50] who states that: "Quick acting barbiturates (nembutal and seconal) are most lethal; slowly acting barbiturates (phenobarbital) are less lethal." The intermediate and short-acting barbiturates have an immediate effect following absorption; whereas, with the longer-acting barbiturates there is a latent period even after intravenous injection of the drug. Hence, it follows that in view of the delayed action of the long-acting barbiturates, it is physically possible to ingest larger amounts of these compounds. It should also be pointed out that none of these patients developed pulmonary complications.

Seconal. Eleven cases of seconal poisoning are reviewed in Table 5. The dose ingested varied from 11 to 97 mg. per kg. Patient 3, who succumbed, ingested 33 mg. per kg., received no analeptic therapy and presented hyperpyrexia as a complication of her barbiturate intoxication.

Comment. The average oral fatal dose of seconal for man has been estimated to be between 14 and 20 mg. per kg.; while for cats and dogs the oral LD_{50} is reported to be about 50 mg. per kg. Since all the patients, except the one previously mentioned, ingested a dose greater than 20 mg. per kg. and received some form of analeptic therapy, it is difficult to arrive at any definite opinions regarding the average oral fatal dose. Since the 4 patients who received amphetamine and disodium succinate ingested only from 17 to 26 mg. per kg. of seconal, one cannot make any claims regarding their efficacy. Picrotoxin was administered in effective concentrations in 4 cases, and metrazol in 1. Patients 5 and 9 ingested 97 and 65 mg. per kg. of seconal and received 926 and 585 mg. of picrotoxin respectively. In only these 2 cases is there indubitable proof of the effectiveness of the picrotoxin therapy.

Mixtures of Barbiturates. Table 6 reviews 11 cases of poisoning with mixtures of barbiturates. Eight recovered and 3 died. Special attention is called to Case 6—a woman who ingested 178 mg. per kg. of barbital and 45 mg. per kg. of phenobarbital. In this patient picrotoxin caused a striking return to consciousness on several occasions, but finally the patient succumbed to pneumonia. This indicates that the analeptics may clinically antagonize barbiturate depression but do not chemically replace these depressants or increase their rate of destruction or elimination. In every case picrotoxin was given in what appears to be effective amounts. Case 2 may be an example of a harmful effect of the analeptic, although it must be admitted that the patient for some reason developed cerebral edema. Anoxia may well have been induced by secondary depression caused by an over-stimulation of the central nervous system by analeptic therapy.

Comment. There are 3 types of intoxicating barbiturate mixtures: 1) long-acting, 2) short-acting, and 3) long and short-acting. Cases 1, 4, 5, 6, and 7 represent mixtures of 21 long-acting barbiturates; Case 2 a mixture of intermediate and short-acting barbiturates; and Cases 3, 8, 9, 10, and 11 a combination of 1 long-acting and 1 short-acting barbiturate. Certainly from what has been previously stated, one might well expect that the most toxic combination would be the one containing 2 long-acting barbiturates. As a matter of fact, of the 5 who ingested such mixtures, 2 succumbed. It is interesting to note that in both cases picrotoxin caused a striking return of consciousness. Patient 2 ingested a mixture of amytal and nembutal but died apparently of cerebral edema. It should also be stated that the relative dosage is important. It is assumed, of course, that

the barbiturates are additive synergists, and at the present time not enough is known regarding the nature of this synergism to conclude whether or not any or all of these cases would have recovered without specific analeptic therapy. None of the patients reviewed, with the possible exception of Cases 1, 2, 3, 4, 6, and 7, ingested significant amounts of any of the barbiturates. It appears that in Cases 1, 3, and 4 picrotoxin exerted life-saving effects.

Discussion. In this paper an attempt has been made to analyze reported cases of acute barbiturate intoxication. Papers on this subject published during the past 15 years from which no instructive or practical information could be extracted were deliberately omitted. While no claims are made that all cases have been recorded, we feel that the group described is representative and provides sufficient data to formulate definite concepts regarding this problem.

A general review of the data discloses that 68% of the patients reported were women and that the median age of this group was 33 years; 32% were males, and their median age was 38 years.

Twenty-four of the 88 cases developed pneumonia. Of these, 11 patients had pneumonia despite chemotherapy, and 13 had pneumonia and no chemotherapy. Two patients had chemotherapy and no pneumonia. Sixty-two patients had no chemotherapy and no pneumonia. We do not wish to imply that random chemotherapy is contraindicated in acute barbiturate poisoning, but merely maintain that the literature does not support the theory that it is an absolute prophylactic measure. While penicillin is generally recommended in doses from 25,000 to 50,000 units every 3 hours, one should not be complacent and hesitate to use other chemotherapeutic agents if signs of pneumonia become manifest. For example, in one of the cases to be discussed, pneumonia developed despite the administration of penicillin but responded subsequently to aureomycin therapy. The best preventive treatment for pneumonia is adequate specific analeptic therapy, as the early awakening of the patient prevents the pulmonary complications. The data show that the more prolonged the coma (central nervous depression) the more frequently are pulmonary complications encountered.

An analysis of the data discloses that in less than 50% of the cases that received analeptic therapy, it was not indicated. The mere fact that an individual is completely anesthetized with barbiturates does not necessarily indicate that he is a candidate for specific analeptic therapy. We do not entirely agree that the classification of barbiturate coma according to states and grades presents a true indication of the depth of barbiturate depression since even the Grade IV stage (corneal anesthesia and absent reflexes) has been clinically reproduced by Lundy[33] with sodium amytal and is being reproduced in anesthetic practice with thiopental sodium with or without premedication. How can one then determine the need for analeptic therapy? In our opinion, the best indication is the response of the patient to a single intravenous injection of 5 cc. of 10% metrazol. Some patients, although to all appearances typical representatives of the Grade IV stage, awaken immediately following such a dose. On the other extreme there are patients whose only response to this dose is a barely noticeable respiratory stimulation. The orientation dose should never be given unless there is presumptive evidence that the patient is poisoned with barbiturate or some other aliphatic narcotic. If one is uncertain and definite proof cannot be established, then the orientation dose

of metrazol should be given slowly and discontinued upon the appearance of twitches about the body. The orientation dose employed for awakening of lightly barbiturized patients is about the average minimum convulsant dose for humans. It should be realized that in patients poisoned with aliphatic narcotics in general, and barbiturates in particular, there exists a wide margin of safety; that is, a relatively small dose of barbiturate will physiologically antagonize a large dose of a central stimulant, such as metrazol. Patients anesthetized with barbiturates have sufficient concentration of these drugs in their central nervous system to prevent serious convulsions from this orientation dose.

Although, generally speaking, the blood level is a good indication of the concentration of barbiturates in the central nervous system, certain exceptions were observed by Koppanyi and Dille[26]. In some cases the concentration of barbiturate in the central nervous system may be much higher than the blood level would indicate. This statement should not be construed to disregard the value of the blood level as a criterion for the depth of barbiturate narcosis but rather to question a dogmatic statement recently made[17] that barbiturate coma cannot exist in the absence of detectable barbiturate in the plasma—the interpretation being in this case that the cause of the coma is no longer the physical presence of barbiturate in the central nervous system, but reversible or irreversible damage of the central nervous structures. If this were so, analeptic therapy would, of course, be contraindicated. As a matter of fact, the evidence in the literature of barbiturate coma co-existing with complete elimination of the barbiturate is based only on blood level determinations and does not exclude the presence of barbiturate in the central nervous system. There is little, if any, evidence for irreversible central nervous system damage inflicted by barbiturates except in cases of certain brominated barbiturate derivatives[31].

It may be disastrous to neglect a patient who has taken large quantities of barbiturates on the supposition that by means of one or the other chemical tests one is unable to detect the presence of barbiturates in the plasma. It is instructive to review a case that did not respond to an orientation dose of metrazol.

Case Report. The patient, a 52-year-old white male, was found in a comatose state following the ingestion of a dose of phenobarbital estimated to be approximately 10 gm. (143 mg. per kg.). Immediately on admission the patient was given 6 cc. of metrazol intravenously with no awakening effect. This was followed by 13 cc. of 0.3% solution of picrotoxin at the rate of 1 mg. a minute until the knee jerks returned. Since the vital signs were good, picrotoxin was discontinued, and the patient was given only symptomatic therapy, which consisted of penicillin, oxygen, and forced fluids. On the 3rd day of admission, the patient was still comatose, his temperature had risen to 104° F., and Roentgen-ray examination disclosed bilateral basilar pneumonitis. The patient was bronchoscoped, aspirated, and placed in an oxygen tent. It was decided to reinstitute analeptic therapy, and he was given 5 cc. of 0.3% solution of picrotoxin every 15 minutes over a period of 1½ hours. The patient responded with purposeful voluntary movements. Twelve hours later he would not respond to stimuli. Then he was given 5 cc. of picrotoxin (0.3% solution) each hour over a period of 3 hours. The patient gradually became more alert, and because of the persistent elevated temperature he was given aureomycin. He made a complete recovery on the 9th day after admission.

This case illustrates (as do several others recently observed but not included in the tables) the importance of constant analeptic therapy when indicated and the dire effects of placing too much faith in good symptomatic therapy alone. We feel quite certain that had this patient been given picrotoxin at regular intervals from

the time of his admission, the duration of his coma would have been reduced considerably and the complication of pneumonitis avoided. Of course, there are some who advocate that good symptomatic therapy is preferable to analeptic treatment whether or not barbiturates are present in the plasma. Even disregarding the impressive experimental data, the analyses of the cases published in this report reveal that a physician in charge of a patient with severe barbiturate poisoning who fails to avail himself of metrazol and picrotoxin and depends on merely nonspecific general supportive therapy takes a great deal of responsibility on himself.

Those cases which respond to the orientation dose with temporary or permanent complete awakening require only good symptomatic care. Those who respond only with purposeful movements and a return of reflexes will require additional metrazol until their awakening is complete. In cases with no response to the orientation dose except for some medullary stimulation, intensive analeptic therapy is indicated (picrotoxin). If the precaution in giving an orientation dose had been observed in every case of barbiturate poisoning here reported, our task of evaluating the efficacy of the various analeptics would have been easier. We are quite certain that in many of the cases complete awakening would have resulted from an orientation dose and that the patients would have recovered without any further analeptic therapy. In our opinion, the experimental evidence that animals can be protected from multiple fatal doses of long and short-acting barbiturates by the intravenous administration of picrotoxin or metrazol is alone sufficient to refute the claims that the administration of these analeptics does not have a life-saving effect and that good symptomatic therapy alone suffices.

Analeptics, particularly in cases of not too severe barbiturate poisoning, have an awakening or denarcotizing effect with or without latent periods. The term "awakening" is preferred to "denarcotization", as there is no evidence for either a chemical antagonism between analeptics and barbiturates or even that the analeptics accelerate the essential elimination of the barbiturates. Analeptics are not only awakening but also life-saving agents in barbiturate poisoning. It is important to emphasize that a patient may be treated with analeptics for days without dramatic awakening. In this latter event the analeptic maintains adequate circulation, respiration, metabolism, and body temperature during the period of acute depression of the central nervous system by barbiturates.

In assessing the value of analeptics as life-saving agents in the patient with barbiturate poisoning, the question of what constitutes an oral fatal dose of the offending barbiturate in humans necessarily arises. Only if we have an approximate knowledge of the oral LD_{50} for man can we come to any definite conclusions regarding the efficacy of the various analeptics.

The reported cases of untreated barbiturate poisoning are few and far between so that reliable data regarding this question are difficult to obtain. Hambourger made an attempt to establish the oral LD_{50} for various barbiturates in man. From the cases reviewed and the additional data now available, it becomes apparent that his figures must be revised. Fairly accurate data are available regarding the oral LD_{50} of the various barbiturates in the larger laboratory animals. While there is no reason to believe that the LD_{50} for animals and man are identical, a relationship between animal and human fatal doses may be established by

comparing the relative efficacy or toxicity of various barbiturates used in animals and in humans as surgical anesthetic agents.

It is a matter of record that the larger doses of some barbiturates occasionally, and others very frequently, have been used in therapy or for anesthesia. Phenobarbital in doses of from 25 to 30 mg. per kg. orally has been employed as a basal anesthetic before nitrous oxide or ethylene administration, particularly before thyroidectomies. Also, sodium phenobarbital has been given intravenously in similar doses in status epilepticus. These amounts have never produced any serious toxic effects but only sedation or semi-anesthesia. Lundy[33] produced anesthesia in humans with intravenously administered sodium amytal in doses from 25 to 40 mg. per kg. of body weight, and in 3 cases he even gave 50 mg. per kg. followed by recovery. He distinctly states, however, that the latter dose may be considered a pre-mortem dose. In the dog the average anesthetic dose varies from 40 to 60 mg. per kg.; whereas, the LD_{50} is about 70 mg. per kg. Lundy's results agree with the figures published by N. F. Paxson[41], and Zerfas *et al.*[51].

Thiopental sodium is frequently used to produce surgical anesthesia both in experimental animals and the human patient. Fortunately data are available not only as to the amounts necessary to produce surgical anesthesia in animals and in humans, but also as to the plasma levels necessary for first and second plane anesthesia. Peterson, Gould and Shideman[42], administering this barbiturate intravenously at the rate of 70 mg. per kg. per hour, found that about 2.32 mg. per 100 cc. is necessary for the production of corneal anesthesia, while Jailer and Goldbaum[23] have demonstrated that in human patients without premedication, thiopental sodium when infused at the rate of approximately 35 mg. per kg. per hour produces satisfactory first-plane surgical anesthesia at about the same blood level, while the second-plane anesthesia appeared at blood levels between 2 and 3 mg. per 100 cc. It may, therefore, be concluded that Hambourger's data as to the fatal doses of different barbiturates for the human are, as a rule, too low, and if we reason by analogy, the toxic and fatal doses of barbiturates for humans (unless some unforeseen complications develop) are not less than one-half the corresponding dose for large laboratory mammals. This, however, is only important insofar as the statistical evaluation of the physiological antidotes in the treatment of acute barbiturate poisoning is concerned. It has no bearing whatsoever on the problem of when and where specific analeptic therapy in barbiturate poisoning is indicated. In comatose patients we are obviously not concerned with the LD_{50} of any given barbiturate but rather with the possible LD_1 of the offending barbiturate. The LD_1 of a barbiturate can be, of course, as low or even lower than Hambourger's figures indicate, and if a patient is anesthetized and does not respond to an orientation dose, then regardless of the amount of barbiturate ingested energetic treatment is indicated.

If the patient does not respond to an orientation dose of metrazol, the depth of the central nervous system depression is such that one may also observe absent corneal reflex, hypothermia (unless fever exists from various causes), circulatory or respiratory depression, and demonstrated high blood or urinary levels of barbiturates. As much as we would like to indicate the minimum oral dose per kg. requiring treatment, we do not feel that it would be practical to do so because of the unreliability of the history. Analeptic therapy may be contraindi-

cated in cases where the above conditions do not prevail, for the simple reason that the concentrations of the barbiturates may be insufficient to protect the central nervous system from a large dose of these convulsants. In fact, we may refer to one case in this report (Table 4, Case 7) which not only did not require an analeptic but had to be tranquilized with chloral hydrate.

Central stimulants are indicated in only one type of central nervous system depression; namely, the one precipitated by aliphatic depressants because the latter afford a protection against the convulsant effects of analeptics or render convulsions harmless if they occur. The explanation of the latter appears to be, as Gold and Travell have shown[20], that the cause of death in convulsions is the exhaustion and fatigue of the respiratory center, and if the threshold of the center is raised by aliphatic narcotics, the experimental animals may convulse for long periods of time. However, such convulsions do not terminate fatally in contrast to convulsions produced by similar doses of central stimulants in unprotected animals who die within a short time following the first signs of convulsive spasm. Central depression caused by hypoglycemia, various types of anoxia, and by opiates, should not be treated with analeptics because in these types of depressions the central nervous system is not protected from the harmful effects of the analeptics. In case of morphine poisoning a subconvulsant dose of a central analeptic may actually precipitate convulsions[22].

There have been reports in the literature concerning the use of intravenous sodium succinate in the treatment of barbiturate poisoning. In fairly concentrated solutions, coughing and flushing in the blush areas immediately follows its injection. Shortly thereafter, definite and dramatic analeptic responses are reported to occur. The cases of barbiturate poisoning treated with this drug cannot be taken as conclusive of the efficacy of such therapy. Most of the cases reported ingested such relatively small amounts of barbiturates that analeptic therapy was not indicated, and it is regrettable that the 2 cases of barbital poisoning that may have ingested significant amounts of the drug are presented so that no definite conclusions can be drawn regarding the specific action of the alleged antidote (Table 1, Cases 13 and 14). In one case the patient was a known psychopath who received picrotoxin prior to disodium succinate. The other patient, according to the report upon her recovery, stated that she had taken 0.3 gm. of nembutal and 1 oz. of elixir of phenobarbital. However, 2 hours later she recalled having taken 150 phenobarbital tablets with the other hypnotics. Aside from the fact that even if one accepts the estimated figures of the barbiturate intake of these cases, most of them are not within the fatal range so that the only action that can be claimed for this antidote would be an awakening rather than a life-saving action. The well-controlled experimental studies in animals[11] did not show either awakening or life-saving effects after the administration of succinate. The conclusions of Corson and co-workers have been recently confirmed by Zuckerbrod *et al*[52] in human material. Since in some animal experiments and in human cases succinate was given in highly concentrated solutions, it is quite possible that the cough and even the analeptic effects were due to its irritant action on the responsive structures (Cattell[8]).

Amphetamine and dextrotatory amphetamine are respiratory and vasomotor stimulants, and there are publications indicating that these substances in large concentrations exert

a beneficial effect in barbiturate poisoning. A review of the cases herein reported will not permit us to come to any definite conclusion regarding their efficacy. In experimental animals (unpublished data, Koppanyi) amphetamine has neither an awakening nor a lifesaving effect in severe barbiturate poisoning. Unfortunately, one cannot conclude from the human data presented that amphetamine exerted a life-saving effect. Only one of the patients receiving amphetamine succumbed. This patient ingested 57 mg. per kg. of amytal (Table 3), developed pneumonia, and died on the 2nd day. It may be interesting to point out in comparison that Patient 1, who ingested 156 mg. per kg. of the same barbiturate, recovered even though he received only insignificant amounts of picrotoxin.

It may be argued that picrotoxin and amphetamine should be used simultaneously in the treatment of acute barbiturate intoxication since amphetamine is primarily a cortical stimulant and picrotoxin and metrazol are subcortical and spinal excitants. Such a combination will have an awakening and, in addition, a general central stimulating effect. However, anyone who has seen a patient depressed by barbiturates awaken immediately following the injection of metrazol, or within 15 minutes after the injection of picrotoxin, would not doubt that these analeptics are also cortical stimulants in barbiturate poisoning. In other words, they antagonize the action of barbiturates wherever these depressants act and not by selective stimulation of specific nerve centers.

Caffeine and coramine were resorted to in several of our cases. With these drugs there is neither clinical nor experimental evidence which could justify their use in the treatment of severe barbiturate poisoning.

Both *in vitro* and *in vivo* studies have demonstrated that the barbiturates decrease the cerebral metabolic rate. This depression is presumably due to an inhibition of certain enzyme systems concerned with the oxidation of carbohydrate by the central nervous system. The administration of picrotoxin[30] will overcome the depressing effects of the barbiturate on the central nervous system. A restoration of the cerebral metabolic rate is obviously desirable in barbiturate poisoning. We do not feel that with a normal oxygen saturation of the arterial blood and a normal cerebral blood flow the increased demands for oxygen resulting from the picrotoxin injection will produce any deleterious effects on the organism. Kety[24] has demonstrated, however, that a decrease in the cerebral metabolic rate may follow a convulsive seizure. It should be obvious, therefore, that in the treatment of barbiturate poisoning excessive central nervous system stimulation (convulsions) is definitely contraindicated since the ensuing depression added to that resulting from the barbiturate poisoning may be more than the organism can tolerate.

It is a common experience to hear fear expressed on the part of the medical profession to use potentially convulsant drugs in the treatment of barbiturate poisoning. This fear is somewhat paradoxical, as metrazol and electric shock are freely being used to produce convulsions in unprotected individuals. The protective action of barbiturate against convulsive agents has already been pointed out. To consider other possible objections to the use of metrazol and picrotoxin in the treatment of acute barbiturate intoxication, one might also consider the fact that picrotoxin and metrazol may, in addition to their stimulating action, produce depression[13]. This depression is characterized by a loss of placement reactions and appears to be independ-

ent of convulsions or it appears before convulsive attacks and lasts some time afterwards. Mousel and Essex[38] reported that rabbits anesthetized with 25 mg. per kg. body weight of pentothal sodium recover in 75 to 82 minutes when given 15 mg. per kg. of metrazol or 0.2 mg. per kg. of picrotoxin, as compared to the average recovery time of the controls—66 minutes. It is to be noted that these doses are negligible in comparison to the doses used by Koppanyi, Linegar and Dille[28] in experimental animals (metrazol, 50 mg. per kg. or higher; picrotoxin, 4 mg. per kg. or higher). It is very likely that the increase of the duration of the barbiturate anesthesia observed by Mousel and Essex was due to the factor already noted by Dille and Hazleton. It certainly has nothing to do either with the awakening or the life-saving effect of metrazol or picrotoxin.

If the patient reacts favorably to the orientation dose (partial awakening effect, that is, coordinated voluntary movements, return of corneal reflexes, increase in muscle tone, favorable respiration and circulation response), then metrazol should be the agent of choice and should be continued (5 cc. of 10% solution) every 10 or 15 minutes until complete awakening results. If the patient does not react favorably to the first or to repeated doses of metrazol, picrotoxin therapy should be instituted with the usual dose levels. An initial dose of 25 mg. is given by vein and 15 mg. in a similar manner every 15 minutes until there is evidence of either complete awakening or at least a return of reflexes. Then the dose of picrotoxin should be reduced but medication should not be discontinued until the patient is able to perform purposeful, voluntary movements.

In the majority of cases the physician will find that metrazol is the drug of choice for the ultra-short, short-acting, and intermediate-acting barbiturates. In cases of poisoning resulting from massive doses of short-intermediate or of long-acting barbiturates, picrotoxin is the drug of choice. Massive doses of intermediate-acting or even short-acting barbiturates, as previously indicated, act as long-acting barbiturates since the high concentration precludes rapid essential elimination.

We do not contend that the employment of central nervous system stimulants are the final word in the treatment of barbiturate poisoning. Further research should be undertaken to find other antidotal measures. There are 2 papers which may point the way for further clinical study: a) massive intravenous infusion which resulted in life-saving but not awakening effects from several fatal doses of barbiturate in animal experiments[12], and b) the studies of Koppanyi and Linegar[27] which showed that cross-circulating small dogs severely poisoned by barbital with large normal dogs may save the life of the barbiturate-poisoned animal. These studies suggest distinct possibilities for exchange transfusions or dialysis with an artificial kidney.

Summary and Conclusions. 1. Analysis of 88 cases of acute human barbiturate poisoning reveals that picrotoxin exerted a definite life-saving action.

2. There is no conclusive evidence to indicate that amphetamine, coramine, disodium succinate, and caffeine exert a life-saving action in barbiturate poisoning.

3. Many cases of human barbiturate poisoning treated with analeptics do not require specific treatment and will recover with adequate symptomatic care.

4. To differentiate between patients requiring energetic picrotoxin or met

razol medication and patients not requiring analeptic therapy, it is advised that an orientation dose (5 cc. of 10% of metrazol solution) be administered intravenously. If the patient responds favorably to metrazol, only symptomatic care is indicated.

5. The objection that analeptics unduly stimulate an already depressed central nervous system is not well founded since aliphatic hypnotics protect against multiple fatal doses of the analeptics. The other objection that these stimulants excessively increase the oxygen demand of the central nervous system and thus cause an additive depression is also untenable.

6. Central stimulants are contraindicated in comas produced by central nervous system depressions other than those caused by barbiturates or other aliphatic hypnotics.

7. The average fatal doses for humans currently quoted in the literature are far too low. A better approximation of the average fatal dose may be derived by comparing the semianesthetic or anesthetic dose of various barbiturates in experimental animals and humans. It is pointed out, however, that the knowledge of the oral LD_{50} for humans of the various barbiturates is important only for the statistical evaluation of the antidotes. Once the necessity for an effective antidote is established, a patient receiving an LD_1 of a given barbiturate may require the same type of energetic treatment as one ingesting an LD_{99}.

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RADIOLOGY

UNDER THE CHARGE OF

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PITUITARY TUMORS

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DURING the past several years, considerable progress has been made in the development of radiologic methods for the diagnosis and treatment of pituitary tumors. Through new advances in radiation therapy, it now appears possible to arrest the growth potential of many of the most frequently occurring pituitary adenomas for considerable periods of time. Also, new techniques in roentgen diagnosis have been reported which permit the diagnosis of these lesions at appreciably earlier times than have heretofore been possible. In view of these and other developments, it has seemed profitable to review the radiologic and associated literature pertaining to the pituitary gland.

Pituitary tumors comprise approximately 10% of the neoplasms of the brain[18]. In general, they are of 2 principal types, the adenomas and the craniopharyngiomas. The former make up approximately 70% of the total and arise from mature cellular elements of the gland. They are classified as: a) chromophobe, b) acidophil, and c) basophil. The craniopharyngiomas, comprising about 30% of all pituitary tumors, are congenital cysts arising from remnants of Rathke's pouch and usually are suprasellar in location. In addition, a number of other tumors including adenocarcinomas and rarely adamantinomas[4] have also been recorded.

Among the pituitary tumors, chromophobe adenomas are the most frequently occurring. In Cushing's series reported by Henderson[20], two-thirds of the lesions were of this type and subsequent communications from Kerr[26], Bachman and Harris[3] and Davidoff and Feiring[7] present similar figures. These tumors arise most commonly during the fourth and fifth decade of life; however, many cases have been reported in much younger and much older age groups.

Acidophil tumors comprise about 25% of the adenomatous lesions of the pituitary gland. Like the chromophobe tumors they occur most frequently in adult life; their peak incidence, however, occurs approximately a decade earlier. Both chromophobe and acidophil adenomas demonstrate an almost equal sex distribution.

Basophil adenomas are relatively

rare. In Cushing's series[32] they comprised less than 2% of the total, and more recent figures by other authors are not significantly different. Unlike chromophobe and acidophil lesions, basophil adenomas appear to have a strong predilection for the female sex. A compilation of the data collected from Sosman[32], Kerr[26], Bachman and Harris[3], and Davidoff and Feiring[7] indicate that 5 are seen in females for every 1 in males.

The craniopharyngiomas are lesions which occur principally in childhood. However, their presence in the adult should not be overlooked. Grant[18] in a series of 30 cases reported that 60% were discovered after the age of 24.

Clinical Manifestations and Roentgen Findings. The clinical manifestations, including the roentgen findings, of the 3 adenomatous lesions and of the craniopharyngiomas differ markedly from one another. The acidophil and basophil cells of the pituitary gland possess endocrine activity and accordingly adenomatous tumors of either cell type produce marked constitutional symptoms of hyperpituitarism at a relatively early stage before the lesions have acquired great size. The chromophobe cells on the other hand have no secretory function, and tumors of this cell type produce symptoms and clinical findings that result from compression of neighboring structures. Among these are the normal pituitary cells surrounding the tumor. It therefore is not uncommon to find changes that reflect a hypopituitary state in chromophobe lesions[24].

a) *Chromophobe Adenomas.* Chromophobe adenomas are particularly prone to expand the sella turcica and protrude beyond its confines[20]. Early in the disease, the growth extends just sufficiently above the sella turcica to cause compression of the optic chiasma; impairment of vision therefore soon follows. As the lesion continues to grow, it may expand in several directions. It may break through the bony floor of the sella turcica into the sphenoid air cells and the nasopharynx. At other times it extends laterally through the dura below the temporal lobe of the brain. Such an extension is likely to cause little pressure on the chiasma and under these circumstances the lesion produces few symptoms until it becomes quite large. Most often, the tumor continues to grow upward through the diaphragma sellae where if it remains unchecked it becomes so large as to obliterate the 3rd ventricle and to displace the basal ganglia forward. When an adenoma has extended beyond the limits of the pituitary gland, it is enclosed by a condensation of its own substance which serves to delimit it from adjacent structures. When the lesion lies wholly within the pituitary gland, however, it possesses no limiting capsule[20].

The expansile characteristics of chromophobe adenomas lead ultimately to ophthalmologic, neurologic, roentgenologic and endocrine disturbances. In all probability the earliest changes are roentgenologic, since the tumor must extend considerably beyond the confines of the sella turcica before ophthalmologic and neurologic changes can occur and since endocrine disturbances also do not develop until the degree of compression is severe. However, since roentgen examinations are not performed until subjective symptoms appear, the early roentgen changes usually go unnoticed.

The typical ophthalmologic finding is a bitemporal hemianopsia accompanied by failing vision[8,30,37]. Often, however, the visual disturbance is more bizarre and may assume one of a number of forms representing an involvement of one of the optic nerves or of one of the optic tracts or a combination of these with chiasmal defects

in addition. One sometimes finds therefore homonymous defects, often asymmetrical in nature and accompanied by central scotomata. Also unilateral blindness with defects in the remaining field or possibly nasal or temporal hemianopsia accompanied by defects in the contralateral eye are other variations that have been observed. The type of defect depends on whether the lesion is prechiasmal, chiasmal or postchiasmal.

The neurologic manifestations of chromophobe adenomas beyond those referable to the optic nerves and tracts occur when the lesion has become large. Upward extension of the tumor may result in encroachment upon the third ventricle and subsequent obstruction of the ventricular system. All of the evidence of increased intracranial pressure will then follow. Lateral extension of the tumor may involve the ocular nerves with varying degrees of ophthalmoplegia. When the extension progresses beneath the temporal lobes of the cerebral hemispheres, aphasia may be encountered.

The endocrine changes of chromophobe adenomas, which are those of hypopituitarism, as Hurxthal and Younghusband[24] have pointed out, not infrequently precede the ophthalmologic manifestations. Pressure on the hypothalamus in females leads rapidly to amenorrhea, and pressure atrophy of the basophilic elements of the pituitary gland produces among other things a diminution of the sex hormones in the urine. Loss of sexual hair including body, axillary, pubic, facial and aural hair also occurs, particularly when the hypopituitarism is marked. The diminished activity of the pituitary gland leads also to changes in the hemopoietic symptom, the thyroid gland and the adrenal glands. A normocytic type of anemia which fails to respond to iron therapy may occur. The basal metabolic rate may fall, although the patient remains alert and does not present the usual facies of a myxedematous person. The loss of pituitary function affects the adrenal glands in a number of ways. Hypoglycemic reactions with coma may occur. These changes are accompanied by a low blood-sugar curve during the glucose tolerance test and by a marked insulin sensitivity when the hypopituitarism is severe. Diminution of blood pressure also occurs when the production of desoxycorticosterone falls.

The principal roentgenologic disturbance of chromophobe adenomas is an enlargement of the sella turcica. The enlargement is characteristically uniform, thereby causing a ballooned appearance. In addition, the walls of the sella turcica are thinned and the posterior clinoid processes are frequently displaced upward and posteriorly. They too are thinned and show evidence of pressure decalcification.

The normal dimensions of the adult sella turcica when seen in the lateral roentgenogram of the skull are approximately 10.5 mm. in the anteroposterior direction and 8.5 mm. in the depth[23,28]. Pancoast *et al.*[30] regard any sella turcica to be pathologically enlarged if these dimensions are greater than 12 mm. and 10 mm., respectively. In a series of chromophobe adenomas reported by Hueblein[23] the average anteroposterior dimension was 23 mm. and the average depth was 17 mm.

Most of the cases in Hueblein's series were seen soon after the development of symptoms. It therefore appears that considerable enlargement of the sella turcica occurs before the onset of symptoms in patients with chromophobe adenomas. This observation is supported by pathological studies conducted several years ago by Jefferson[25] in which it was shown that pituitary adenomas must rise a minimum of 2 cm. above the diaphragma sellae be-

fore they encroach on the optic chiasma and cause visual disturbance. In view of this evidence it seems entirely possible that many adenomas of the pituitary gland may be detected by sellar mensuration before clinical symptoms appear and at a time when the results of therapy are likely to be most successful. This possibility has recently led Hare[19] and his colleagues to make a careful study of the sellar dimensions of apparently healthy persons in order that the range of normal sellar size might be more precisely delineated and the detection of early pathological changes more easily made.

In Hare's investigation, 700 cases, of both childhood and adult age groups, were examined with stereoscopic roentgenograms of the skull in 2 projections. In one, conventional lateral roentgenograms were made, with care being exercised to expose one of the stereoscopic films in a so-called "exact" lateral position. This was done to reduce the distortion of the floor of the sella turcica as far as possible. The 1st film was exposed by directing the roentgen beam 2 cm. posterior to the outer canthus of the eye just above the zygomatic arch; the 2nd film was taken with a cephalad shift of 3.5 inches and with a 5 degree caudal tilt of the roentgen tube. The other set of stereoscopic films was made in a posteroanterior projection with the patient in an upright position. In the 1st film, the roentgen beam was directed through the skull 0.5 inch above the level of the external auditory meatus. On the 2nd film the tube was moved downward 3.5 inches and angled 5 degrees cephalad.

From the various films that were made, Hare and his colleagues measured the lateral plane area of the sella turcica, the distance between the anterior clinoid processes, the distance between the posterior clinoid processes, the width of the dorsum sellae and the width of the floor of the sella turcica for each of the patients examined. The data in children were apparently not reliable for any of these dimensions except the lateral plane area and were omitted from the report. The average values of the lateral plane area of the sella turcica in the various age groups are shown in Table 1; also included are the ranges that were observed. The adult data for the remaining dimensions are shown in Table 2.

TABLE 1.—FRONTAL PLANE AREA OF SELLA TURCICA IN RELATION TO AGE

Age	*Average sq. mm.*	*Range sq. mm.*
1	28	26 to 38
3	48	38 to 58
10	60	45 to 75
19 and over	74	50 to 100

TABLE 2.—OTHER DIMENSIONS OF SELLA TURCICA

	Average mm.	*Range mm.*
Distance between anterior clinoid processes	26	Upper limit—28
Distance between posterior clinoid processes	18	15 to 20
Width of dorsum sellae	15	9 to 18
Width of sellar floor	15	9 to 23

In the adult, the average value of the lateral plane area of the sella turcica is 74 sq. mm. (range 50 to 100 sq. mm.). Hare arbitrarily placed the dividing line between a normal and an abnormal sella turcica at a value of 130 sq. mm. It is difficult to learn from Hare's report whether or not this value is entirely justified, as detailed statistical results were not published. We shall have to await future publications for clarification of this point. However, of particular interest in Hare's study is the recent finding of 28 patients with lateral plane areas of the sella turcica in excess of 130 sq. mm. and who presented no clinical evidence of a pituitary adenoma. These cases may

represent exceptions to the normal range of sellar size listed in Table 1. However, it is also possible that these patients have chromophobe adenomas which have been discovered in a presymptomatic stage. This seems particularly so in view of Costello's[5] recent study of autopsied material in which an extremely high incidence of asymptomatic pituitary tumors of one cell type or another was reported. Hare and his colleagues are following their patients with periodic clinical and roentgen examinations. It is hoped that all may be followed until the status of the pituitary gland is completely determined in them.

The extent to which a chromophobe adenoma has expanded beyond the sella turcica can be determined most satisfactorily by ventriculography[7]. Tumors which extend in a cephalad direction encroach upon the cisterna interpeduncularis and displace it posteriorly. In addition, the cisterna chiasmatis is displaced rostrally and not infrequently is obliterated entirely. Large tumors also cause deformation of the hypothalmic portion of the 3rd ventricle and even cause obstruction of the ventricular system at the aqueduct of Sylvius. When this latter finding occurs, the increased intracranial pressure which follows requires immediate surgical intervention. Tumors which extend laterally under the temporal lobe produce changes in the temporal horn on the ipsolateral side with cephalad displacement of the third ventricle. Many other changes in the ventricular system have also been recorded for tumors whose size and position do not follow the usual pattern. These findings are not usually difficult to evaluate when they are considered in relation to other clinical findings.

Difficulties sometimes arise in distinguishing chromophobe adenomas from parasellar and metasellar lesions such as meningiomas, aneurysms of the circle of Willis, gliomas of the optic chiasma, and tumors which obstruct the aqueduct of Sylvius[23]. All of these lesions often produce some enlargement of the sella turcica. The suprasellar meningiomas however usually produce a hyperostosis of the tuberculum sellae and of the lesser wing of the sphenoid. Also, enlargement of the sella itself is minimal in extent and of course there is no evidence of hypopituitarism in the patient. On pneumoencephalography one observes displacement of the cephalic margin of the cisterna interpeduncularis caudally and truncation of the frontal horns of the lateral ventricles.

Aneurysm of the circle of Willis characteristically produces sudden ophthalmoplegia and pain about the eye and forehead but such symptoms may be caused by a large chromophobe adenoma in which hemorrhage has occurred. The identification of so-called curvilinear streaks of calcification lateral to the sella turcica will strongly support the diagnosis of aneurysm, however. This calcification usually takes the form of double striae on a level with or just above the caroticoclinoid foramen. Hueblein[23] has described the calcification as having a convex upward curvature representing the arch of the carotid siphon. The most satisfactory method for differentiating a chromophobe adenoma from an aneurysm of the circle of Willis however is through the use of angiography of the skull. The injection of the opaque material should of course be performed on the same side as that of the suspected lesion.

Gliomas of the optic chiasma and nerves usually occur in childhood, and evidence of neurofibromatosis can often be found elsewhere in the body[7]. Roentgenographic studies of the long bones and pelvis may be profitable in the identification of such widespread

lesions. When the sella turcica is involved, the anterior clinoid processes are usually undermined, thereby leading to a J-shaped sella turcica[23]. Enlargement of the optic foramen can often be identified and pneumoencephalographic studies will reveal obliteration of the cisterna chiasmatis and slight deformity of the cephalic border of the cisterna interpeduncularis.

The correct diagnosis of metasellar lesions which produce obstruction of the aqueduct of Sylvius is often extremely difficult, the sellar changes produced by such pathological processes frequently being similar to those due to chromophobe adenomas. However, the dorsum sellae and posterior clinoid processes are eroded from above in metasellar lesions[30]. Furthermore, the posterior clinoid processes frequently become pointed and shortened rather than uniformly thinned.

b) *Acidophil Adenomas.* The acidophil cells of the pituitary gland are the source of growth promoting hormones. Thus patients with acidophil adenomas in contrast to those with chromophobe tumors show the endocrine effects of hyperpituitarism. These are gigantism in children and acromegaly in adults.

Acidophil adenomas rarely grow to the size of chromophobe lesions. Therefore the symptoms and changes of pressure on neighboring structures produced by the former are less striking than those of the latter. Indeed, the ophthalmologic and neurologic manifestations of acidophil adenomas are often minimal in extent. Less than half of the patients suffer from visual failure and often the most striking complaint is headache[26].

The over-production of growth hormones leads to characteristic bodily changes which usually render the diagnosis obvious at a glance. The head becomes large, the jaws prognathic and maloccluded, the nose prominent and the tongue thickened. The extremities are large, the shoulders rounded and the hands spadelike and puffy. The hair is abundant and coarse, the skin is thick and perspiration is excessive. Also, the overgrowth is not limited to the skeleton, as many think, but involves all of the viscera and probably all body tissues[5].

Concurrently with the overproduction of growth hormones, there is often an overabundance of other pituitary secretions including the thyrotropic and some poorly defined anti-insulin factor. These changes cause an increase in the basal metabolic rate, excessive menstruation or increased libido and potentio in the male and decreased sugar tolerance sometimes accompanied by glycosuria.

In contrast to the patient with a chromophobe tumor, the acromegalic is often obstreperous, uncooperative and difficult to handle. Such manifestations are also not infrequently accompanied by marked mental disturbance. These patients, too, often complain of so-called waves of acromegalism with exacerbations and remissions of their symptoms for no obvious reason.

About 20% of the patients having pituitary adenomas present evidence of a mixture of acidophil and chromophobe elements. In the beginning the signs and symptoms of such patients are the same as those of the typical acromegalic. Later, however, the development of acromegaly stops and the state of hyperpituitarism gives way to a state of hypopituitarism. Cushing[6] has called this syndrome, "fugitive acromegaly", and explained it by postulating that the chromophobe cells outgrow the acidophil cells and eventually arrest their function by compression. When this occurs, the subsequent course of the patient is that of a person having a simple chromophobe lesion.

In acromegaly, 3 types of roentgen-

ologic disturbances have been described in the sella turcica[30]. In one, the sellar enlargement is minimal, but typical bone condensation may be visualized in the calvarium. In the 2nd, a ballooned appearance is present as in chromophobe tumors; the dorsum sellae however is thicker and denser than normal. In the 3rd, extensive destruction of the sella is found; this occurs when the tumor is large.

In addition to the sellar changes, there are a number of other roentgenologic findings which are more typical. The calvarium is large, dense and thickened with prominence of the supraorbital ridges. There is striking hyperpneumatization of the paranasal sinuses. Also, the mandible is hypertrophied with malocclusion of the jaws and wide spacing of the teeth. Tufting of the ungual tuberosities of the hands is often marked. Indeed, Holt and Hodges[22] believe that overgrowth of the terminal phalangeal tufts, prominence of the bony tuberances along the shafts of the metacarpals and phalanges and a peculiar soap-bubble pattern of distorted trabeculae in the bone ends are so typical of an acidophil adenoma that its diagnosis may be suspected even in the absence of changes in the skull.

c) *Basophil Adenomas.* The basophil cells of the anterior lobe of the pituitary gland secrete a hormone known as the adrenocorticotropic hormone. This hormone acts directly on the cortex of the adrenal glands. In the absence of a responsive adrenal cortex it does not exert any known metabolic effect within the body. In basophil adenomas there is an overproduction of adrenocorticotropic hormone which leads to a hyperplasia of the adrenal cortex and an excessive secretion of cortical hormones.

At least 3 groups of hormones arise from the adrenal cortex. There are those which preserve the sodium and water balance of the patient and thereby regulate the state of hydration, blood volume and blood pressure[14,35]. This so-called salt hormone is present in moderate excess in patients with basophil adenomas. Also secreted is a group of hormones closely related to the male sex hormones of the testes which contribute to the secondary male characteristics and assist in the formation of muscle tissue at the expense of carbohydrate and fat formation[14]. For reasons that are not well understood, this hormone is not greatly increased when excessive stimulation from a basophil adenoma occurs. There is finally a group of hormones known as corticoids which counteract the androgenic hormones. They lead to the formation of carbohydrate and fat at the expense of muscle tissue and bone matrix[1]. Liver glycogen, blood sugar and fat deposits are increased, muscle tissue is depleted and osteoporosis occurs. The corticoid hormones also have a regulatory effect on the hemopoietic system. Lymphoid tissue is suppressed, circulating eosinophils are decreased and neutrophils are increased[10,21].

In view of the complex relationships between the adrenocorticotropic hormone of the pituitary gland and the cortical hormones of the adrenal glands, the symptoms and laboratory findings of patients with basophil adenomas are most bizarre. The former include a peculiar adiposity which spares the extremities, cyanosis of the hands, feet, face and neck, amenorrhea in the female and loss of libido and potentio in the male, muscular weakness, drowsiness or depression, thinning and dehydration of the skin often accompanied by pigmentation, polyphagia, polydipsia and polyuria and hypertension.

The laboratory findings may be divided into those associated with the urine and with the blood. Among the

former may be included a glycosuria, an albuminuria and occasionally a hypercalcinuria. Also in the urine is a mild increase in 17-ketosteroid concentration, and a greatly increased excretion of corticosteroids. Urinary creatinine excretion is usually low. In the blood there is a neutrophil leukocytosis, a lymphopenia and an eosinopenia. Also a low phosphorus level and a high calcium content are observed.

The foregoing signs and symptoms vary somewhat in prominence depending on which type of adrenal hormone predominates. It should also be pointed out at this time that the syndrome may be produced not only by a basophil adenoma of the pituitary gland but by a primary adenoma of the adrenal cortex or by a tumor of the primordial cells of the ovary such as an arrhenoblastoma. The excessive secretion of adrenocorticotropic hormone which is characteristic of basophil tumors however leads usually to an increased corticoid secretion and the rather typical loss of protoplasm, fat formation and diabetes.

The roentgenologic findings of basophil adenomas include a limited osteoporosis of the skeleton and occasionally lithiasis of the urinary tract[32]. Most but not all patients exhibit a true osteoporosis of the skull, spine, pelvis and ribs, with sparing of the extremities. In the development of this osteoporosis there is an inability of the bones to form and lay down protein matrix. This condition therefore is quite different from osteomalacia where there is an inability of the body to deposit calcium in the matrix and from osteitis fibrosa cystica where there is excessive loss of calcium from bone.

The skull exhibits the fine diffuse mottlings of a generalized osteoporosis. There are no localized lesions and there is no evidence of increased intracranial pressure. The sella turcica is almost always normal in size and shape since the profound systemic disturbances of hyperpituitarism occur well before the tumor grows to a large size. Fuller and Russell[17] however have reported 2 cases with sellar enlargement in which the basophilism was also accompanied by chromophobe neoplasia. Sosman[32] has also reported that the lamina dura around the teeth is intact in contrast to the situation in osteitis fibrosa cystica of hyperparathyroidism where it is absent.

Not infrequently, there may be spontaneous fractures of the ribs and vertebral bodies with a dorsal kyphosis often following the latter disturbance. The rib fractures may exhibit excessive callous about them. Sussman and Copeland[33] reported that when the fractures and the resulting callous are near the anterior ends of the ribs, there is a characteristic broadening or flaring of the ribs on the roentgenogram.

Differentiation of basophil adenomas of the pituitary gland and tumors of the adrenal cortex may often be made by roentgenologic examination of the abdomen. A definite tumor mass in the suprarenal region may often be seen in the latter condition. There may also be downward displacement of the ipsolateral kidney or elevation of the ipsolateral leaf of the diaphragm. As we have previously noted, the abdominal roentgenograms may sometimes reveal small renal calculi. Sosman[32] also found calcified gall stones in 2 of 7 cases he reviewed. Both changes presumably follow the hypercalcemia that exists in the basophilic state.

d) *Craniopharyngiomas.* Craniopharyngiomas are cystic tumors, teratomatous in character, which arise from remnants of Rathke's pouch. They are suprasellar in position and produce symptoms through pressure on adjacent structures including the hypo-

thalamus, the optic nerves and tracts, the floor of the 3rd ventricle and the pituitary gland. Pressure on the pituitary gland leads to the development of hypopituitarism as in chromophobe adenomas.

In children where craniopharyngiomas are found most frequently the endocrine changes give rise to adiposity, dwarfism and sexual infantilism as described by Frohlich[16]. In the adult the changes are often not greatly dissimilar to those produced by chromophobe tumors and accordingly make their differential diagnosis rather difficult. Encroachment upon the optic pathways produces serious visual disturbance and papilledema. Blindness frequently follows if the pressure is not relieved by operation.

Seventy percent[29] of craniopharyngiomas are sufficiently calcified to cast a recognizable shadow on lateral roentgenograms of the skull. In most of these cases there is also enlargement of the sella turcica. Indeed sellar enlargement of some degree is present in the majority of patients. The enlargement is accompanied by atrophy of the floor of the sella turcica and by erosion and depression of the posterior clinoid processes. Pneumoencephalographic studies reveal a deformity of the third ventricle, particularly in the region of the hypothalamus, obliteration of the cisterna interpeduncularis and a defect of the rostral end of the cisterna pontis[7].

In children there is usually little difficulty in the diagnosis of craniopharyngiomas. The differentiation of these lesions from chromophobe adenomas in the adult may, as we have said, be difficult. This is particularly so when suprasellar calcification is absent. Occasionally surgical exploration must be followed before the diagnosis is made. Fortunately, craniopharyngiomas are infrequent in the age groups where chromophobe adenomas are common.

Treatment. Tumors of the pituitary gland are for the most part benign lesions. Nevertheless, there is always a certain urgency for the institution of therapy, as serious neurologic problems or generalized endocrine disturbances are usually present at the time of their discovery.

In general, acidophilic and basophilic adenomas are most satisfactorily attacked by radiation therapy. The evidence of recent work also indicates that radiation therapy with certain well defined exceptions is the primary treatment of choice in chromophobe adenomas. The therapy for craniopharyngiomas is exclusively surgical since these lesions do not respond to radiation.

a) *Chromophobe Adenomas.* In almost all instances the primary therapeutic problem of a chromophobe adenoma is the relief of pressure on adjacent structures, usually the optic chiasma, optic nerves or optic tracts. It is therefore not surprising that surgical evacuation of the tumor was widely accepted for many years as the primary therapeutic procedure in patients with this lesion. Indeed, the immediate results of surgery have often been excellent since removal of even portions of the lesion yield relief of the ophthalmologic and other neurologic changes that may be present. In Cushing's series of cases reported by Henderson[20], immediate improvement in vision was observed in 72% of the patients who were treated by surgery. In this group of cases, both the transphenoidal approach and the transfrontal operation were used with the results of each procedure being equal to one another.

Unfortunately, the surgical methods that may be applied to the pituitary gland are not without considerable risk. Although Cushing was able to

establish an operative mortality of only slightly in excess of 2%, such a low level has rarely been achieved in other clinics. Grant[18] at the University of Pennsylvania reports an operative mortality in excess of 9% and others have even higher rates.

Unfortunately, too, chromophobe adenomas do not have a well defined capsule which might permit the complete enucleation of the tumor at surgery. As a result, only portions of the lesion can be removed and undetermined fractions of the tumor remain behind. As a result many surgically treated chromophobe tumors recur. Indeed, in Henderson's series 50% of the chromophobe tumors exhibited a return of symptoms within 5 years of therapy.

In an effort to reduce the growth potential of the cells remaining after surgery, Cushing instituted a therapeutic program in which surgery was followed by radiation therapy. The results of this procedure have been eminently satisfactory with the number of cases without recurrence after 5 years rising to 87% if the transfrontal approach is used and 65% if the transphenoidal operation is employed.

Concurrently, with the development of surgical techniques, other workers were applying radiation therapy to the problem of chromophobe tumors[9,12,13]. At first, the results were discouraging. Radiation damage to the brain was feared and the dosages of radiation which were administered to the lesions were small. When brain damage did not occur, however, dosages were increased and the results have improved. Indeed, Kerr[26,27], and Bushman and Harris[3] have recently been able to cause regression of the symptoms in almost 60% of their cases for periods of 5 years or more. Such results are closely comparable to those yielded by surgery plus post-operative radiation particularly when it is remembered that there is no mortality associated with radiation therapy.

The method of treatment currently used by Kerr[26], and Bachman and Harris[3] consists of the radiation of 4 fields directed toward the sella turcica —2 temporal, 1 frontal and 1 vertical. The radiation employed is of relatively short wavelength in order to reduce as far as possible the skin dose received at each of the portals. Kerr suggests the use of 200 kvp., a quality of 1.95 mm. Cu. half-value-layer, a 50 cm. tube-skin distance and a 5 cm. cone. Such a combination of factors may be easily obtained with almost any of the roentgen therapy units available today.

A relatively low dosage of 100 roentgens is given to one field on the first day in order to reduce as much as possible the chances of the tumor's swelling and causing increased intracranial pressure and headache. If there is no reaction, 100 r are given to each of 2 fields on the 2nd day. After this, 200 r are given to each of 2 fields per day until a total of 2000 r are administered to each field. All dosage measurements are made in air.

The dosage delivered to the tumor with the foregoing technique is of the order of 2400 r. A somewhat greater dosage (3000 to 3600 r) may be administered if portals of 6 by 8 cm. are employed. In either case epilation of the hair over the treated areas occurs; however, this phenomenon is entirely temporary.

Using the foregoing technique Kerr has been able to increase the visual fields, reduce the headache and generally improve the patient's condition for a period of 5 years in 58% of his cases. Arrest of the ophthalmologic changes and loss of the headache have been achieved for a similar period in an additional 12%. The results have been poor in 30%.

The cause of failure in these patients in whom the results have been un-

satisfactory has been the subject of some speculation. When the dosages applied to pituitary tumors were appreciably less than those advocated today, the percentage failure was considerably greater than that recorded by Kerr. This may lead one to ask whether even greater dosages should be applied in the future. This may be so. However, it should be pointed out that approximately 20% of chromophobe adenomas are cystic in character and cystic lesions have little or no response to roentgen radiation. Also, a certain number of the lesions are likely to be radio-resistant to therapy. It therefore may be expected that about 30% of chromophobe adenomas will not respond satisfactorily and that present-day radiation dosages are probably adequate.

Before the recent trend toward higher radiation dosages, radiation treatment was frequently administered in several courses, many weeks apart. Also, if the lesion did not respond properly, the program of therapy often was repeated. It is always difficult to evaluate the benefits of such modifications in the therapy schedule, but Bachman and Harris[3] have recently been able to do so in a review of their patients. In general, their results of therapy were disappointing where the radiation was divided into multiple courses or where the radiation was repeated for a recurrence of the lesion. Certainly, little seemed to be gained by not following the simple technique in which 3000 roentgens were delivered to the tumor within a period of 30 to 45 days.

Although one may usually proceed with the administration of roentgen therapy without great concern, Kerr[26] points out 3 instances where one must use caution or defer to the surgeon. These include 1) suspicion of a cystic tumor; 2) symptoms of hemorrhage into the tumor, and 3) increased intracranial pressure.

Cystic lesions, as we have said before, respond poorly to radiation and it therefore may be argued that surgery should be employed without the delay of a course of radiation therapy where such changes are suspected. Unfortunately, there is almost no way in which one can be certain that cystic degeneration has taken place in a chromophobe adenoma without radiation or surgical interference. In view of this, Bachman and Harris[3] and also Kerr[2] proceed with the institution of radiation in all cases where hemorrhage or increased intracranial pressure have not occurred. As the course of radiation is given, perimetric studies of the visual fields are meticulously followed. If at the end of 2 months a satisfactory response has not been achieved, the lesion is taken to be either cystic or radio-resistant, and the patient is referred to the neurosurgeon.

It is usually not difficult to suspect hemorrhage in a chromophobe tumor since there is frequently a history of a recent acute episode in which severe visual disturbances are manifested. When such an episode occurs, surgery should be employed quickly since rapid visual degeneration may otherwise occur.

The increased dosage of radiation advocated for pituitary tumors raises questions concerning the possible damage to the cranium and cranial contents. A number of cases of necrosis of the skull following the irradiation of pituitary tumors has been reported[26]. As Kerr has shown, however, this complication can be effectively avoided if multiple ports of therapy are employed and if radiation of reasonably high penetrability is used. Certainly no bone damage may be expected if a dose of only 2000 to 3000 roentgens to each portal is given.

The same may also be said of the

possible damage to the brain. The examination at autopsy of patients who received large quantities of radiation for brain tumors indicates that it is very difficult to produce any anatomical change within the brain by irradiation of the type used in conventional medical practice. Also there is no evidence to indicate that serious functional disturbance occurs following irradiation.

b) *Acidophil Adenomas.* The treatment of acidophilic lesions like those of the chromophobe variety is directed toward the limitation of the growth potential of the tumor cells and the relief of pressure produced by the adenoma on surrounding structures. Usually the latter problem is of secondary importance because these tumors usually create severe systemic disturbance before they encroach on neighboring structures.

When roentgen dosages similar to those employed for chromophobe adenomas are used, the progress of the lesion is usually arrested. In Kerr's experience failure in the treatment of acidophil adenomas occurs principally when the tumor is cystic or hemorrhagic. The prognosis in such cases appears to be rather poor, both from the radiologic and surgical standpoints.

c) *Basophil Adenomas.* The treatment of basophil adenomas has recently been summarized by Sosman[32]. In general, 2 lines of attack may be employed. In one, measures to counteract the effects of the pituitary-adrenal axis may be instituted. In the other, direct attack may be made on the secretory activities of the pituitary's basophilic cells or of the cells of the adrenal cortex. In the first approach the prolonged administration of testosterone has been instituted by some workers in an attempt to counteract the excessive secretion of the corticoid hormones. This approach[1,15,38], however, has not been very successful. In the second approach, estrogens[15,31] have been given in an effort to suppress the activity of the basophil cells. Although a few good temporary results have been achieved, the long-range effects of this therapy have been disappointing, also.

In addition to the use of estrogens, irradiation of the pituitary region, irradiation of the adrenal areas, partial adrenalectomy and occasionally surgery of the pituitary gland have been employed. As far as the surgical methods are concerned, the results are extremely discouraging. In the case of adrenalectomy, the procedure is usually followed by cortical insufficiency[59], and death.

Probably more patients have been benefited and more prolonged remissions of symptoms have been obtained by the use of radiation therapy of the pituitary region than by any other method. It must be emphasized, however, that good results of lasting character have been obtained in only a small percentage of the patients. Complete and lasting remissions are extremely rare and all too often even temporary relief is not obtained.

The techniques that have been employed in the radiation of basophil lesions have been extremely variable. Some workers have used small dosages of a few hundred roentgens. Others have administered 2000 to 3000 r to the tumor. The results that have been achieved seem to have no relationship to the dosage applied, a fact that suggests that radiation like other forms of therapy is of little value; the few good results that have been obtained may easily be due to the peculiar tendency of the disease to cyclic variations and spontaneous remissions[2,34]. However, the number of cases that have received adequate radiation (that is, 3000 to 4000 r) to the pituitary has been small and therefore it may be well to reserve judgment on radiation

therapy until more data have been collected.

d) *Craniopharyngiomas.* Since craniopharyngiomas are cystic lesions, they are unresponsive to radiation therapy and therefore must be attacked by surgical methods. Unfortunately, these tumors are frequently entangled in adjacent vascular structures including the internal carotid and anterior cerebral arteries. Accordingly, their removal is often fraught with great difficulties and at times is completely impossible. Under these circumstances the prognosis of the lesion is discouraging and the operative mortality is high[18].

Discussion. Among the various pituitary tumors, the outlook for the chromophobe adenoma is the most satisfactory. Either radiation therapy or surgery, or a combination of the two, controls the local effects of the lesion in a high percentages of cases, and the systemic endocrine manifestations are usually minimal in extent. Furthermore, it now appears that the tumor may be diagnosed in its presymptomatic state at a time when therapy is most successful by means of roentgenologic studies of the sella turcica. The evidence at hand indicates that a chromophobe adenoma expands the sella turcica long before it assumes a sufficient size to encroach upon adjacent neurologic tissues. Therefore, a patient with an enlarged sella turcica (that is, one greater than 130 sq. mm. in its lateral plane area) should be suspected of having a chromophobe adenoma even in the absence of visual or other symptoms. Of course, one should not consider the institution of radiation therapy or surgery in such an individual without further study. However, therapy of one kind or another should be undertaken if subsequent roentgenograms of the skull taken after an interval of 3 to 6 months demonstrate an additional increase in sellar size, even though symptoms have not yet appeared. Radiation therapy instituted at this time will almost certainly cause permanent regression of the lesion and will avoid the dangers which follow further growth of the tumor.

It is fortunate that chromophobe adenomas comprise over 50% of pituitary tumors, for the prognoses of the remaining lesions of the gland are rather discouraging. This is particularly so in the case of the basophil adenoma. It appears that until much more is known of the secretory activity of the basophil cells, the control of this type of tumor will remain a serious problem.

In recent years, little or no progress has been made in the development of methods by which the acidophil adenoma or the craniopharyngioma may be combatted more successfully. Radiation methods appear to have gone as far as they are able in the case of the former lesion and surgery seems to have reached its maximum position in the case of the craniopharyngioma. Earlier diagnosis may well be the key to the solution of the problems which these tumors pose. In this connection it does not seem that better diagnostic methods are required as much as the earlier appearance of the patient at the office of his physician for the application of the methods now at our disposal.

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BOOK REVIEWS AND NOTICES

THE CEREBRAL CORTEX OF MAN. By WILDER PENFIELD, M.D., Prof. of Neurology and Neurosurgery, McGill Univ., and THEODORE RASMUSSEN, M.D., Prof. of Neurosurgery, Univ. of Chicago. Pp. 248; 120 ills. New York: Macmillan, 1950. Price, $6.50.

IT is easy to predict that this comprehensive book will become a standard work in the laboratory and library of everyone interested in the human cerebral cortex. It is written in the spirit of Sherrington's School. It gives in precise and readable form the source material gained from clinical, electroencephalographic and electrocorticographic observations in patients and from results of cortical electrical stimulations and extirpations during almost 400 craniectomies. The conclusions are carefully drawn, and the Authors have avoided indulgence in any hypotheses. This new doctrine of localization of function in the human cortex makes fascinating reading. It is shown that the body surface is distributed on the central convolutions according to functional importance and that the two central convolutions represent a sensory-motor unit. The border lines of the cortical fields seem to be less precise, functionally and histologically, than was so far presumed, and no vestige of the suppressor strips was found. Secondary acoustic, optic and sensory-motor fields are mapped. The appearance of dreamy states, blackout of memories and temporary suppression of naming objects and of counting on stimulation of circumscribed areas gives a new approach to many aspects of brain physiology. F. L.

MEDICAL GYNECOLOGY. By JAMES C. JANNEY, M.D., Assoc. Prof. of Gynecology, Boston Univ. 2d ed. Pp. 454; 108 ills. Phila.: W. B. Saunders, 1950. Price, $6.50.

ACCORDING to the Author this edition has 2 aims: to aid medical students in correlating didactic lectures with clinical experience and to provide refresher material for the general practitioner.

The volume is divided into 7 sections consisting of history and examination, symptomatology, abnormal physical findings, tests and special examinations, treatment, socio-medical problems and the choice between irradiation and operation. While all sections are well done, except for the brevity of the section upon physical findings, the 2nd and the 6th sections are particularly good.

That devoted to the patient's complaints reflects abundant clinical experience and thoughtful organization. The consideration of each of the common gynecological complaints contains a brief and lucid tabulation of the most important differential diagnostic points.

The section upon socio-medical problems is divided into 4 sub-sections: environmental factors, contraception, preparation for marriage, and marital maladjustments. Each topic is considered in such a sound and understanding manner that this chapter enhances the worth of the volume tremendously. As the Editor states, "What we have lacked until the past few years has been the marriage counselor, the general practitioner of marriage, who is equally competent to handle all of the problems and who has to refer to specialized help only on rare occasions".

The book is prepared attractively and has an accurate index and bibliography. The gross illustrations are *apropos* and clear. The usefulness of the microscopic illustrations of cervical and endometrial changes is questionable, however. A more complete consideration of abnormal physical findings by both discussion and gross illustration would have been helpful.

This volume will aid the student in obtaining a broader view of the subject of gynecology, will furnish the general practitioner with needed refresher material, and will also impress the busy specialist with the importance of the many socio-medical problems in gynecology which so many of us have neglected, either through lack of time and understanding or through the lack of training.

F. P.

A SHORT TEXTBOOK OF RADIOTHERAPY. By J. WALTER, M.R.C.P. (Lond.), and H. MILLER, Ph.D. (Camb.). Pp. 444; 199 ills. Phila.: Blakiston, 1950. Price, $6.00.

THIS short textbook contains material pertinent to many phases of clinical radiotherapy, including physical principles, natural and artificial radioactive substances and radiotherapy in dermatology. Though not definitive, there is a quantity of useful fundamental information embraced in the short chapters covering wide fields. Primarily intended for students and technicians, it would also seem a valuable review source for radiologists and a good introduction to radiotherapy for physicians not primarily interested in radiology. E. P.

MODERN TRENDS IN ORTHOPAEDICS. Edited by SIR HARRY PLATT, M.D., Prof. of Orthopaedic Surgery, Univ. of Manchester, England. Pp. 497; 222 ills. New York: P. B. Hoeber, 1950. Price, $10.00.

THIS timely and informative book by Platt and his collaborators discusses a wide range of orthopaedic problems and is an excellent resumé of the current thought of this specialty in England. It should be in the library of every orthopedic surgeon, for it is well written and adequately illustrated; it may be taken as an index of the high intellectual caliber of the Authors represented. P. C.

PSYCHOSOMATIC MEDICINE, ITS PRINCIPLES AND APPLICATIONS. By FRANZ ALEXANDER, M.D., Clinical Prof. of Psychiatry, Univ. of Illinois, with a Chapter by THERESE BENEDEK, M.D. Pp. 300. New York: W. W. Norton, 1950. Price, $4.00.

AN outgrowth of Dr. Alexander's earlier work, "The Medical Value of Psychoanalysis", this book describes the concepts on which the psychosomatic approach in medicine is based and presents the results of study concerning the influence of emotions on bodily processes in health and disease. Dr. Alexander, as a leader in American psychiatry and psychoanalysis and as one who has been outstanding in his contributions to the field of psychosomatic medicine, is eminently qualified to write such a book. It is an important contribution in this day and age, which has been referred to as the "psychosomatic era in medicine". It will be of real interest and use to physicians, psychiatrists, medical students and others working in the medical field.

W. P.

BIOLOGICAL STUDIES WITH POLONIUM, RADIUM, AND PLUTONIUM. Edited by ROBERT M. FINK, Ph.D., Assoc. Clin. Prof. of Physiological Chemistry, Univ. of California. Pp. 411. New York: McGraw-Hill, 1950. Price, $3.75.

THIS volume is one of a series being compiled of the research work done during the war years under the Manhattan Project and the Atomic Energy Commission. When this series is completed it will consist of some 60 volumes; this one reports the experimental studies carried out by the Biological Chemistry Section of the division of radioactivity in the Manhattan Department of the University of Rochester. Polonium, radium and plutonium are all alpha particle emitters, and the purpose of this study is a comparison of the biological effects of these similar radioactive elements. For one engaged in fundamental biological chemical research this volume is of value. Most of this experimental work was of necessity clothed in secrecy during the war years, and with the publication of this data a great deal of reduplication of work will be avoided. E. P.

A SHORT HISTORY OF PHYSIOLOGY. By KENNETH J. FRANKLIN, D.M., Prof. of Physiology, St. Bartholomew's Hospital. 2d ed. Pp. 147; 16 ills. London and New York: Staples Press, 1950. Price, $2.00.

THIS edition gains much over the 1st—brought out in war time—by its better design, better paper and cover, and the inclusion of 16 halftone portraits of physiologists and a frontispiece. The 1st edition could not be illustrated. There are also scattered additions to an otherwise almost verbatim reproduction of the original text. In spite of its small size, the book is loaded with facts—overloaded perhaps, as there is a noticeable tendency to dry staccato sequences. It is, however, a welcomed follower of Foster's now aged History.

E. K.

SUPERVOLTAGE ROENTGENTHERAPY. By FRANZ BUSCHKE, M.D., SIMEON T. CANTRIL, M.D., and HERBERT M. PARKER, M.Sc., Tumor Inst., Swedish Hospital, Seattle. Pp. 375; 260 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $10.50.

THIS short book is a brief report of the Authors' 8 years experience with radiotherapy in the 800 kv range. In the 1st chapter, a description of the equipment and an explanation of the biophysical differences and advantages of voltages in the higher ranges are outlined. The remaining 10 chapters emphasize the clinical and therapeutic problems in the treatment of various forms of malignancy.

This monograph is an unbiased evaluation of the usefulness of supervoltage therapy. Chiefly, in the major forms of cancer, supervoltage treatment is tolerated considerably better; there is less morbidity due to the treatment itself and sequellae are reduced. There is no attempt to establish a definitive group of results through statistics. Numerous well illustrated clinical histories are presented and evaluations are left to the reader. A commendable feature of the text is the critical analysis of limitations of radiotherapy in cancer, not only in the supervoltage ranges but in the more widely used 200 kv range, which considerations are not fully emphasized in many standard works that show trends toward over-enthusiasm. E. P.

MEDICAL PHYSICS. Vol. 2. Editor-in-Chief, OTTO GLASSER, Ph.D., F.A.C.R. Pp. 1227; 978 ills. Chicago: Year Book Publishers, 1950. Price, $25.00.

THE present volume is a complement and supplement to the 1st volume which was issued in 1944, and reprinted in 1947. (Reviewed in the Am. J. Med. Sci., **207**, 697, 1944.) This is an entirely new work, containing only material which either was not covered in the 1st volume or which, because of advances in knowledge, required new presentation. Subject matter which has remained essentially unchanged has not been reprinted, but is referred to by title.

The subjects are arranged in alphabetical order; a comprehensive index serves for ease of reference. As in the earlier volume, the field covered includes not only medicine in its clinical and pre-clinical aspects, but many auxiliary branches of biology. It is of encyclopedic character, and will no doubt serve as a most useful text of reference. B. L.

The 1949 YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY. Edited by HOWARD T. KARSNER, M.D., Western Reserve Univ., and ARTHUR HAWLEY SANFORD, M.D., Mayo Clinic. Pp. 543; 161 ills. Chicago: Year Book Publishers, 1950. Price, $4.75.

THE present Year Book, like its predecessors, gives abstracts of publications deemed to be of particular interest or significance by the Editors. The abstracts, on the average, are well written and sufficiently detailed; many are accompanied by illustrations, and by brief editorial comments. Where certain recent publications were found to represent only fragments in a series of consecutive studies, the Authors have been requested to present concise reviews of their fields of investigation. The 4 reviews within the present volume deal with: Pathology of atomic bomb casualties, the problem of early cancer, the physiopathology of cancer, and neoplasia in fishes, amphibians and reptiles.

The first half of the book, approximately, deals with pathology, the latter half with clinical pathology. The Editors and publisher deserve congratulations on continuing a worth while text. It gives a cross section of progress in 2 disciplines with which every branch of medicine and surgery is intimately concerned. B. L.

ANNUAL REVIEW OF MEDICINE. Edited by WINDSOR C. CUTTING and HENRY W. NEWMAN, Stanford Univ. School of Med. Vol. 1. Pp. 484. Stanford, Cal.: Annual Reviews. 1950. Price, $6.00.

FOR several years, Annual Reviews have published reviews of biochemistry, physiology and other allied sciences. This volume is the initial endeavor to review the literature on medicine and the sub-specialties. Its Authors have been urged to pitch their writings at a scholarly level, and as a whole this book achieves its purpose.

There has been a very careful selection of authors for each section. This volume should be of particular interest to internists and the busy practitioner interested in the newer advances in medicine and the scientific basis for these advances. The bibliography at the close of each chapter is an extensive and ready reference for those who wish to obtain more detailed information. An excellent feature is the annotated reviews in which the Author of every section lists under each subspecialty the various progress and review articles that have appeared in recent literature, with a one-sentence comment upon each review.

In order to avoid biased interpretations of any particular subject, different authors will be chosen for the reviews yearly so that as subsequent volumes are issued, all attitudes upon controversial subjects will be voiced. The list of authors already selected for 1951 reflects the same excellent choice as shown in this volume. The internist especially should find it of much value to own the series.

J. L.

HANDBOOK OF PHYSICAL MEDICINE AND REHABILITATION. By THE COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION OF THE AMERICAN MEDICAL ASSOCIATION AND 29 CONTRIBUTORS. Pp. 573; 56 ills. Phila.: Blakiston. 1950. Price, $4.25.

WITH the field of physical medicine expanding daily, this volume becomes a 1st edition by the addition of "rehabilitation" to the previous editions of Physical Medicine. This change vastly broadens the scope of the book by bringing under consideration all the medical, psychological and social services with which a person recovering from disease or injury is taught to live.

There are included articles covering the mechanics of physical medicine, such as heat, light, diathermy, fever therapy, massage, hydrotherapy, and electrical currents. In addition are many articles describing the application of these agents to specific diseases, such as fractures, vascular diseases, skin diseases, and psychiatric problems.

This volume should certainly increase one's understanding of the principles and practice of physical medicine. H. V.

THE CRIMINALITY OF WOMEN. By OTTO POLLAK. Pp. 180. Phila.: Univ. of Penna. Press, 1950. Price, $3.50.

This is an excellent presentation of a complex problem. The results, as presented in 11 pages at end of the book, give an excellent analysis of the effects of biological, social and personal factors in a differentiation of male and female conduct disorders in crime. In this respect it will prove of great value to the psychologist, sociologist, and criminologist.

The extensive statistical studies of crime reports in the United States, Great Britain and Continental Europe, while exhaustively done, demonstrate the futility of such mixed statistical studies. For example, prostitution is a crime in the United States and is included in the criminal statistics; it is not so accepted in Continental Europe, yet statistical studies are based upon such a faulty interpretation. While the Author calls attention to this, the results are nevertheless confusing. It appears to the Reviewer that the time and effort spent in the preparation of this volume, if devoted to an analysis of uniform crime statistics from a single source, would prove of greater value.

In the records of the 400,000 cases of the Municipal Court of Philadelphia, covering a period of 30 years, 220,000 are careful detailed studies of delinquent and criminal cases. The material of this Court covers the entire field of criminality. The division of juvenile delinquency, women's criminal division, the men's misdemeanant's division, the women's misdemeanant's division, and the men's criminal division, could give statistics which are uniform in character and based on scientific studies such as would be found nowhere else in the world. An analysis of these statistics would, if added to the present volume in a future edition, make this an outstanding contribution to this subject in the world today. D. McC.

ATLAS OF HUMAN ANATOMY. By M. W. WOERDEMAN, M.D., Prof. of Anatomy, Univ. of Amsterdam. In 2 vols. Plates 512, 642. Phila.: Blakiston, 1950. Price, $18.00.

This entirely new and original atlas consists of 1154 illustrations. All drawings and diagrams are completely labeled but there is no descriptive or explanatory text. The accuracy and high quality of the drawings and their excellent reproduction constitute an important addition to anatomical illustration. Most of the drawings are reproduced without color. The Authors' "guiding principle throughout has been that each separate plate should be a true representation of its physical counterpart", and should show details derived from only one dissection. With several of the heretofore standard atlases of anatomy out of print, this atlas will be a welcome addition to books readily available for teaching and reference. The nomenclature is entirely in Latin and adheres closely to the Basle Nomina Anatomica. R. W.

VESALIUS. THE ILLUSTRATIONS FROM HIS WORKS. By J. B. DeC. M. SAUNDERS, Univ. of California, and CHARLES D. O'MALLEY, Stanford Univ. Pp. 248; 96 ills. Cleveland, Ohio: World Pub. Co., 1950. Price, $10.00.

No small part of the value of this latest 20th century tribute to Vesalius is the 32 page Introduction by these 2 accomplished students of 16th century Anatomy and Medicine and especially of this great figure. With the permission of the New York Academy of Medicine and the Library of the University of Munich, joint publishers of *Andreae Vesalii Bruxellensis Icones Anatomicae*, the Authors have reproduced the illustrations which had been printed from the original wood blocks in 1934, unhappily destroyed by bombs in the recent World War. Ninety-six beautiful full page cuts from the 7 books of the Fabrica, the Epitome, the Venesection Letter, and the Tabula Sex, are presented, each with a translation of Vesalius' own legend (in italics), and annotations by the Authors. Woven into a picture of Vesalius' life, personality and peregrinations are details of his scientific productions, his illustrations, Oporinus the printer, and the political figures who determined the latter phases of his career.

Thus, the Authors achieve their purpose of making available at modest price authentic reproductions of these highly important books with explanations that make them mean more to the reader than do the almost unobtainable originals themselves. Both publishers and authors have made a significant contribution to medical history. E. K.

MODERN PRACTICE IN DERMATOLOGY. Edited by G. B. MITCHELL-HEGGS, M.D., Univ. of London. Pp. 836; 319 ills., 7 color plates. New York: Paul B. Hoeber, 1950. Price $12.50.

MITCHELL-HEGGS has collated the contributions of his 40 collaborators into a unit that should have appeal to certain groups of the American medical public. For the dermatologist this volume, in spite of its size, is rather sketchy and certainly would not serve as a suitable source book. For the

internist and other non-dermatological specialists, there is much well presented material. For the practitioner and medical student the presentation is lucid and superior to the usual compendium or handbook type of exposition.

The Authors of the various sections are, for the most part, younger progressive dermatologists of the British Empire. They have prepared the material in a reasonably uniform manner, but there are some parts of the volume which deserve special mention, namely, Animal Diseases Transmissible to Man; Skin Diseases of Warm Climates; Dermatoses Caused by Protozoal, Bacterial and Virus Infections; Non-Communicable Dermatoses Especially Common in Warm Climates; Disorders of the Skin and Ocular Involvement; Biopsy: its Indications and Technique. Among the more sketchy presentations is that on Syphilis; although written by a recognized authority, the now obsolete division of syphilis into stages is used. Physiotherapy also is given short shrift. H. B.

Sir William Osler Aphorisms. Collected by Robert Bennett Bean, M.D. Edited by William Bennett Bean, M.D. Pp. 159. New York: Henry Schuman, 1950. Price, $2.50.

This devotee's collection of Oslerian aphorisms follows, but in much expanded form, its Editor's "Mosaic" published in the Osler Centennial Number of the Archives of Internal Medicine in July, 1949, and is in no way a repetition of Camac's "Counsels and Ideals". It has an interesting provenance that is described in the Introduction. The 357 items are grouped according to their subject matter into 6 classes (the Medical Student, the Ethos, the Patient, the great Republic of Medicine, Epitomes, Epitaphs). Some of these strike a familiar note, but more are new, at least to the Reviewer—himself an Osler fan—and are often as freshly informal as one would expect in casual remarks by Osler made on hospital rounds. The booklet is well conceived and executed, and will be welcomed on shelves of Osleriana, especially by those who cherish the memory of or wish to know more about this greatest of modern medical humanists. E.K.

Bone and Joint Diseases. By J. Vernon Luck, M.D., Ass't Clinical Prof. of Orthopedic Surgery, Univ. of Southern California. Pp. 640; 703 ills., 21 in color. Springfield, Ill.: Charles C Thomas, 1950. Price, $16.50.

This very interesting book fulfills a need in the correlation of the clinical features of bone and joint diseases to the pathological. It is a practical text that should be of particular value to the Resident in orthopedic surgery as well as the Clinician. It is fairly expensive, but the illustrations, especially the excellent color plates, give a vivid and striking clarity to the text. Dr. Luck is to be congratulated on presenting such a timely and useful book. P.C.

Steroid Hormones. Edited by Edgar S. Gordon. Pp. 396; 117 figs. Madison: Univ. of Wisconsin Press, 1950. Price, $6.50.

A Symposium on Steroid Hormones was held at the University of Wisconsin in September 1948. This book contains the major papers and the proceedings of some of the round table conferences. Leading authorities have presented various aspects of the chemistry, biosynthesis, metabolism and excretion, relation of structure to function and so forth, as well as the biological effects of steroids. This last includes studies of their effect on convalescence, enzyme systems, carcinogenesis, the anterior pituitary and many other facets of the subject. All but a few of the papers have bibliographies. There are many excellent charts and diagrams. Despite the fact that the material was presented 2 years ago, it will be of considerable interest and can be recommended to investigators and students of this vital, rapidly expanding field. F.D.

An Atlas of Human Anatomy. By Barry J. Anson, Ph.D., Prof. of Anatomy, Northwestern Univ. Pp. 518. Phila. W. B. Saunders, 1950. Price, $11.50

For this atlas, the culmination of many years of study and teaching experience, no one is better qualified than Dr. Anson, as is generally agreed to by anatomists. The book is designed for both teaching and reference. It consists of line drawings and half tones, many of them with color, and a few photographs. Brief descriptive text accompanies most of the plates. The book will undoubtedly be widely used and is one of the most important recent additions to this field. R.W.

Principles of Public Health Administration. By John J. Hanlon, M.S., M.D., M.P.H., Assoc. Prof., Univ. of Michigan. Pp. 506; 48 ills. St. Louis: C. V. Mosby, 1950. Price, $6.00.

This book is a timely contribution to the expanding concepts of Public Health. In addition to describing recognized administrative aspects, it considers much broader aspects, such as the philosophy of public health, the

socio-economic justification of public health activities, legal aspects and the relationship between public health and individual medical care. In discussing the customary functions of a health department, the Author not only gives a good description, but often points to possible improvement.

One might wish that Industrial Health were given fuller treatment, also, more of recent data given in certain of the sections, to correspond to the rapid development in the field of public health. Worthy of particular note is the chapter on Socio-economic Justification, in which the Author evolves an intriguing scheme to give a monetary equivalent to health and life and, conversely, to the economic loss due to illness and death.

Here is a very readable book which should be of value, not only to the student and administrator of public health but also to the practicing physician who, together with the health official, is responsible for the health of the public. J.H.

NEW BOOKS

La Lutte contre le Cancer par la Physique nucléaire et l'Acupuncture chinoise. By GERARD BOURGEOIS. Pp. 43. Paris: Librairie Véga, 1950. Price not given.

Neuroses and Sacraments. By ALAN KEENAN, O.F.M. Pp. 163. New York: Sheed and Ward, 1950. Price, $2.50

Colloid Chemistry. Vol. VII. Edited by JEROME ALEXANDER. Pp. 736; illustrated. New York: Reinhold, 1950. Price, $15.00.

Acute Head Injury. By JOSEPH P. EVANS, M.D., Ph.D., Univ. of Cincinnati. American Lect. Ser. 60. Pp. 116; 24 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.25.

Facial Paralysis. By J. PARKES FINDLAY, M.B., Ch.M., Sydney Hosp. Pp. 47; 13 ills. Sydney, Australia: Angus & Robertson, 1950. Price, 17/6.

Freud: Dictionary of Psychoanalysis. Edited by NANDOR FODOR and FRANK GAYNOR. Pp. 208. New York: Philosophical Library, 1950. Price, $3.75.

Sexual Behavior in Society. By DR. ALEX COMFORT, Lecturer in Physiology, London Hospital Medical College. Pp. 154. New York: Viking Press, 1950. Price, $2.75.

Significance of the Body Fluids in Clinical Medicine. By L. H. NEWBURGH, M.D., and ALEXANDER LEAD, M.D. American Lect. Ser. 69. Pp. 76; 15 figs. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

Segment-therapie. VON MAX KIBLER. Pp. 113; 23 ills. Stuttgart, Germany: Marquardt & Cie., 1950. Price, D.M.9.50.

Cerebral Palsy. By JOHN F. POHL, M.D. Pp. 224; 130 ills. St. Paul, Minn.: Bruce Pub. Co., 1950. Price, $5.00.

On the Experimental Morphology of the Adrenal Cortex. By HANS SELYE, M.D., and HELEN STONE, B.Sc., Univ. of Montreal. American Lect. Ser. 74. Pp. 105. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.25.

THIS monograph deals with the Authors' experiments on the effect of dietary variations and hormone injections on weights and histological appearance of adrenals (chiefly in hematoxylin-eosin sections) in rats which usually have been unilaterally nephrectomized. Interpretations of the functional significance of the data will be of interest to those engaged in research on the adrenal. I. T. Z.

Asphyxia Neonatorum. By WILLIAM F. WINDLE, Ph.D., Sc.D., Prof. of Anatomy, Univ. of Penna. American Lect. Ser. 52. Pp. 70, 9 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

THIS booklet consists of a series of lectures dealing with the anatomy, embryology, and physiology of the circulatory and respiratory systems of the fetus and the new born. In addition, there is an account of experimental work done on the problem of asphyxia neonatorum. W. C. S.

NEW EDITIONS

Eyes and Industry (Formerly *Industrial Ophthalmology*). By HEDWIG S. KUHN, M.D. 2d ed. Pp. 378; 151 ills., 3 in color. St. Louis: C. V. Mosby, 1950. Price, $8.50.

Renal Diseases. By E. T. BELL, M.D., Prof. of Pathology, Univ. of Minnesota. 2d ed. Pp. 448; 123 ills., 4 color plates. Phila.: Lea & Febiger, 1950. Price, $8.00.

"No changes have been made in the basic plan of the monograph, but since about 18,000 additional autopsies have been surveyed a larger group of cases of each disease is available for study. The chapters on tubular diseases and extrarenal azotemia have been enlarged. The recent additions to the literature have been incorporated into the text." (Preface.)

McClung's Handbook of Microscopical Technique. Edited by RUTH MCCLUNG JONES, Prof. of Biology, Winthrop College. 3d ed. Pp. 790; 157 ills. New York: P. B. Hoeber, 1950. Price, $12.00.

THIS edition of a well-known and highly useful handbook follows an established pattern, but the subject matter has been regrouped to a more useful arrangement. The book has been expanded by about 40 pages, much of which is given to the first section: General Procedures and Information. The following completely new material has been added: the phase microscope and its applications, preparation of materials for electron microscopy, and discussions of the radio autographic method and polarization microscopy. H. R.